The National Vaccine Advisory Committee

Global Immunizations Working Group

Enhancing the work of the HHS National Vaccine Program in Global Immunizations

Table of Contents

Executive Summary

The global commitment to immunization programs has accomplished unparalleled successes in public health. In 2011, 83% of the world's children received all three doses of the diphtheria-pertussis-tetanus vaccine primary series (DTP3) and routine immunizations now save the lives of approximately 2.5 million children per year. Polio is on track for eradication. Over the past decade, annual measles-related mortality has been reduced by 71% and neonatal deaths from tetanus were reduced by >90%. The world has committed to the common vision of a *Decade of Vaccines* where global efforts are focused on extending the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live. There is much to celebrate, but there is also still much to do.

Vaccine-preventable diseases (VPDs) still account for a quarter of the deaths in children under five. Vaccines against common causes of pneumonia and diarrheal diseases, the leading causes of death in children, are still not widely accessed by developing countries. Children in the lowest wealth quintiles are still the least likely to receive immunizations. Systems for routine immunizations in a number of low- and middle-income countries (LMICs) remain limited in their ability to accommodate new vaccines because of financial and logistical barriers. Countries continue to lack the capacity to collect quality data on the impact of immunization programs, report and evaluate adverse events following immunizations, or detect outbreaks of public health importance. Moreover, vaccines are still unavailable for a number of preventable diseases such as HIV, malaria and other neglected diseases. Despite these challenges, the global community is finding new and innovative ways to solve these issues through international collaborations, public-private partnerships, and sustainable, evidence-based, country-led initiatives.

A recent survey by the Kaiser Family Foundation showed that U.S. global immunization efforts in developing countries are broadly supported by the majority of Americans. But support of global immunizations is not limited to humanitarian aid. Recent threats from infectious diseases such as pandemic influenza or importations of vaccine-preventable diseases such as measles highlight the fact that U.S. health is intricately linked to global health, and efforts to strengthen global immunization systems and reduce the global and economic burden of vaccine preventable diseases have a clear and added benefit for both the U.S. and the global community. The U.S. Department of Health and Human Services (HHS) has responded to this changing environment by supporting strategies and policies that

weave together its mission to protect the health and well-being of Americans with other U.S. government (USG) efforts to bring about a safer and healthier world.

In February 2012, the U.S. Assistant Secretary for Health (ASH) charged the National Vaccine Advisory Committee (NVAC) with *reviewing the role of HHS in global immunizations, the effect of global immunizations on global populations, the effect of global immunizations on U.S. populations, and recommending how HHS can best continue to contribute, consistent with its newly established Global Health Strategy and Goal 5 of the National Vaccine Plan.* The NVAC was also asked *to make recommendations on how to best communicate this information to decision makers and the general public to ensure continued sufficient resources for global vaccination efforts*. The NVAC formed a Global Immunizations Working Group, consisting of experts in issues relevant to all aspects of the global immunization efforts to address this charge.

The NVAC's analysis includes a review of several global initiatives and global efforts to reduce the morbidity and mortality caused by vaccine-preventable diseases through safe and effective immunizations. **This review was not intended to represent an exhaustive catalog of all global immunization activities and as such, this report does not represent the full range of USG efforts that support global immunizations.** Rather, the recommendations developed by the NVAC focus on six areas where HHS efforts should be further leveraged to achieve the greatest contributions to reducing health burdens through global immunization efforts:

1. Tackling time-limited opportunities to complete polio eradication and to advance measles mortality reduction and regional measles/rubella elimination goals
2. Strengthening Global Immunization Systems
3. Enhancing Global Capacity for Vaccine Safety Monitoring and Post-Marketing Surveillance
4. Building Global Immunization Research and Development Capacity
5. Strengthening Capacity for Vaccine Decision Making
6. HHS Leadership and Coordination

NVAC Recommendations

A brief summary of the NVAC's findings under the six key focus areas and the resulting NVAC recommendations are provided below. A more extensive discussion of the background and rationale for each of the recommendations is provided in the full report.

1. Tackling Time-Limited Opportunities to Complete Polio Eradication and to Advance Measles Mortality Reduction and Regional Measles/Rubella Elimination Goals

Global goals including achieving certification of global polio eradication and measles/rubella elimination in at least five WHO regions by 2020 will be important measures of success for the *Decade of Vaccines*. However, progress towards these goals has been threatened by global economic uncertainty, misperceptions regarding the benefits of vaccines and vaccination programs, weak health systems, and violence towards campaign vaccinators. A resurgence of these diseases will have economic and public health consequences that will affect both global and U.S. populations. Though significant technical and financial support has been provided by HHS thus far, better communication of the achievements made, the challenges to completing these goals, and the consequences for failure is needed to garner the continued financial and political support to see these landmark efforts to the finish line.

1.1 The Assistant Secretary for Health (ASH) should communicate to key audiences (including legislators and the general public) the urgency of completing global goals for polio eradication and advancing global measles mortality reduction goals and regional goals for measles/rubella elimination. The ASH should engage these key audiences via briefings, events, and other educational activities.

1.1.1 The ASH should emphasize that polio eradication efforts and measles mortality reduction and regional elimination efforts should complement and strengthen routine immunization systems.

1.1.2 The ASH should emphasize that failure to complete polio eradication goals or to advance goals for measles mortality reduction and regional goals for measles/rubella elimination may threaten the health of US populations due to importations of these diseases from endemic areas.

1.1.3 The ASH should emphasize that political and public support is fundamental to achieving polio eradication and advancing global goals for measles mortality reduction and regional goals for measles/rubella elimination. Achieving these goals would equal a monumental public health and humanitarian accomplishment for the entire global community and if done appropriately, will potentially strengthen support for routine immunization goals.

1.2 The ASH should strongly encourage the HHS Secretary to seek additional funding to facilitate the achievement of unique, time-limited opportunities to complete global goals for polio eradication and to support measles mortality reduction and regional goals for measles/rubella elimination. The ASH should

advocate to the HHS Secretary that completion of these goals will yield significant economic and public health returns on investments and shed new light on the value of vaccines and immunization and the potential for future cost-savings.

1.3 The ASH should encourage the Centers for Disease Control and Prevention (CDC) to continue to enhance the public health impact of its Stop Transmission of Polio (STOP) Program by increasing the number and length of training opportunities. STOP Team assignments should focus on building broad subject matter expertise that can be applied to polio and measles efforts, as well as to strengthen routine immunization systems and disease surveillance.

1.4 The ASH should work with the CDC to create opportunities to bring together stakeholders and leadership from the Global Polio Eradication Initiative (GPEI) and the Measles Rubella Initiative (MRI) to discuss 1) lessons learned and best practices and 2) consider opportunities for joint programming that lead to program efficiencies and improve the delivery of vaccines using routine systems. As a leading partner in both these initiatives, CDC should work to capture and review these findings so as to inform current programming, the introduction of new vaccines, and other global public health efforts.

2. Strengthening Global Immunization Systems

Weak immunization systems jeopardize the substantial investments that have gone into reducing the global burden of vaccine preventable diseases. Prioritizing efforts to strengthen global immunization systems will build long-term capacity for routine immunization systems, ensure equitable access to currently recommended routine immunizations, and accelerate the uptake of new or under-utilized vaccines. HHS provides the greatest contributions towards strengthening global immunization programs by improving data collection systems to maximize the impact of national immunization programs, by building comprehensive and integrated VPD surveillance systems, and by supporting better management, integration and implementation of immunization delivery services.

2.1 The ASH should advocate for HHS efforts that support USAID, GAVI, and multilateral organizations such as WHO and UNICEF in the development of “best practices” and technologies to support countries in their efforts to more accurately track immunization coverage at the national and subnational levels and improve data quality.

2.2 The ASH should work with other HHS offices to develop sustainable support for quality global VPD surveillance systems, including the existing global and regional VPD laboratory surveillance networks. This support ideally should include technical and financial resources needed to support early

warning/outbreak surveillance; laboratory diagnostics; emergency communication systems to detect and respond to outbreaks of VPDs; surveillance requirements for the eradication of targeted VPDs, including case-based polio, measles and rubella surveillance; and laboratory networks to support the introduction and monitor the impact of new and underutilized vaccines.

2.3 The ASH should work with CDC and USAID to increase core support to the CDC's Field Epidemiology and Laboratory Training Program (FELTP) as a key tool to transferring epidemiologic and laboratory capacities for strengthening programs. This support should specifically be used to incorporate immunization topics into FELTP training.

2.4 The ASH should support the work of HHS within the international community to define standards for measuring the impact of routine delivery strategies such as the Reaching Every District/Community (RED/C) strategy. These metrics can be used for the evaluation of how well these strategies perform in fully vaccinating children with routine immunizations.

2.5 The ASH should work with the Office of Global Affairs and CDC to assist national governments, development agencies (including USAID), multilateral organizations (including WHO and UNICEF), and civil society in encouraging the use of immunization contacts (both through routine systems as well as campaign activities) as a platform for delivering additional health and aid services and vice versa. Evaluations of these efforts should include the types of interventions, the cost-benefits of combining new interventions with global immunization efforts, and the effect these strategies have on building community demand for health services overall.

2.6 The ASH should endorse and facilitate HHS coordination with other USG agencies to support efforts that provide routine overseas administration and documentation of vaccinations for all US-bound refugees with vaccines that have been identified for pre-departure administration.

3. Enhancing Global Capacity for Vaccine Safety Monitoring and Post-Marketing Surveillance

As coverage of existing vaccines increases and new and under-utilized vaccines are introduced to larger populations, countries will need support in monitoring, identifying, and responding to vaccine safety concerns and adverse events following immunizations (AEFI). Global approaches to vaccine safety benefit all countries and ongoing efforts are working to overcome the barriers to vaccine safety monitoring that continue to challenge poorly-resourced countries. HHS agencies contribute expertise, training, and the development of standardized tools, guidelines, and processes to enhance global vaccine safety monitoring capacity and help build public trust and demand for vaccines.

3.1 The ASH should identify mechanisms to encourage ongoing collaborations and technical support between HHS agencies involved in post-licensure vaccine safety and related global agencies and partners to 1) enhance capacities to build vaccine safety surveillance systems to monitor the safety of vaccines as they are broadly administered; 2) assess and respond to vaccine safety concerns or signals, 3) effectively communicate vaccine risks; and 4) support the political will to respond to vaccine safety concerns with evidence-based decisions.

4. Building Global Immunization Research and Development Capacity

Continuing HHS commitments to global efforts in scientific discovery and vaccine research and development (R&D) are necessary to address remaining unmet public health needs such as prevention of HIV, tuberculosis, malaria, neglected diseases, and other emerging infectious diseases of global health importance. However, the development of future vaccines, particularly for the prevention of diseases predominately affecting low- and middle-income countries, will require innovative product development partnerships, greater global regulatory capacity, and the growing involvement of emerging vaccine manufacturers in developing countries. HHS support of these efforts will not only increase access to new or improved vaccines and immunization technologies but will also contribute to augmenting global vaccine manufacturing capacity. As a benefit, these efforts will help to achieve national and global influenza pandemic preparedness objectives.

4.1 The ASH should support efforts that increase global health research capacity through partnerships between health research institutions in the U.S. and abroad. These partnerships create opportunities to train the next generation of U.S. and foreign scientists to better address current and future global health needs, including the development and evaluation of new vaccines, new vaccine delivery systems, country-specific immunization schedules, and new technologies that facilitate global immunization efforts.

4.2 The ASH should encourage HHS agencies to work closely with USAID, WHO, GAVI, end-users (including national immunization program managers, Ministries of Health, NITAGs), and vaccine manufacturers to support WHO in their efforts to define vaccine target product profiles.

4.3 The ASH should support NIH and FDA's ongoing efforts to communicate strategies for minimizing barriers to the development of vaccine products. These efforts enhance the identification, testing, and evaluation of promising vaccine candidates to ensure that candidate vaccines advance more quickly through the development pipeline.

4.4 The ASH should support efforts to strengthen national regulatory authorities in other countries through collaborations with the FDA. The ASH should support on-going FDA efforts with other National Regulatory Authorities and the WHO to continue seeking opportunities to inform, shape, and communicate global regulatory standards and requirements for the development and manufacturing of safe and effective vaccines. In doing so, HHS will continue to strengthen international programs, including building and strengthening global regulatory capacity and quality systems.

4.5 The ASH should support HHS agencies in their ongoing efforts to develop training modules and workshops for vaccine manufacturers in developing countries on best practices and approaches for vaccine manufacturing and good manufacturing practices (GMP) guidelines.

5. Strengthening Capacity for Vaccine Decision-Making

The introduction of new and/or underutilized vaccines into national vaccine programs, combined with currently recommended vaccines, has the potential to save 23 million lives by 2020. However, countries are faced with a number of competing public health priorities, and decision-makers must have the capabilities to evaluate the available data to support the introduction of new vaccines into national immunization programs. HHS technical expertise can assist countries in the use of standardized decision analysis tools, technical evaluations, and the engagement of external immunization technical advisory groups to support the adoption of new vaccines into routine programs, to argue for government or donor funding, and to build credibility and acceptance of vaccine policies among the public.

5.1 The ASH should continue to support the development of an evidence base to support informed country-level decisions regarding the development, introduction, and monitoring of new vaccines based on evaluation of disease incidence and prevalence, financial sustainability, vaccine safety and efficacy , cost-benefits, and programmatic considerations.

5.2 The ASH should work with HHS offices and non-HHS partners to increase investments in national evidence-based decision making by National Immunization Technical Advisory Groups (NITAGs) (similar to the US Advisory Committee on Immunization Practices). Support should include technical assistance and provisions to develop and train these national immunization technical advisory bodies.

6. HHS Global Immunization Efforts: Leadership and Coordination

Finally, the full and continued participation of HHS agencies and their staff in global immunization efforts help to build international cooperation towards the common goal of reducing the global burden of vaccine-preventable diseases. Supporting the long-term assignment of HHS personnel to multilateral

organizations, bilateral assignments to support country Ministries of Health, and assignments to public-private global health partnerships ensures that U.S. policies and proposed solutions to global immunization challenges are adequately voiced in the global health arena. Likewise, improving collaborations within HHS agencies in global immunization efforts will ensure efficiencies and a unified focus for HHS contributions towards global immunization programs.

6.1 The ASH should support on-going policy revisions to facilitate long-term assignment of HHS professional staff to international multilateral organizations, bilateral assignments to support country Ministries of Health, assignments to public-private global health partnerships, and other U.S. federal agencies/departments.

6.2 As the director of the National Vaccine Program, the ASH should work with the HHS Secretary, the HHS Office of Global Affairs, and HHS Operating Divisions to define a process to strengthen coordination of HHS-led global immunization efforts. Enhanced coordination would ensure alignment of priorities, minimize duplication in global immunization efforts, support tracking progress in a consistent and transparent manner, and facilitate discussing and addressing challenges and barriers on an ongoing basis.

6.2.1 As part of these efforts, HHS should consider convening an HHS cross-departmental working group to create an HHS Global Immunizations Implementation Plan that includes: measurable outcomes defined by the HHS agencies, how the agencies will track progress towards these outcomes, and potential barriers to achieving the NVAC recommendations and other objectives described in Goal 5 of the National Vaccine Plan.

6.2.2 This HHS cross-departmental working group should also determine a mechanism to enhance HHS coordination with USG agencies (e.g., USAID, U.S. Department of Defense) and other critical non-USG partners (e.g., GAVI Alliance, UNICEF, WHO, the Bill & Melinda Gates Foundation, and others) for improved information sharing and decision-making on USG global immunization activities.

6.2.3 This HHS cross-departmental working group should also collaborate with USG agencies to understand how the whole of USG global immunization efforts are supporting implementation of the Decade of Vaccines Global Vaccine Action Plan, and identify areas where enhanced collaboration can increase the impact of US efforts.

While recognizing that the HHS activities described throughout this report are only one pillar of the USG efforts to strengthen global immunization programs and reduce the global burden of vaccine preventable diseases, the NVAC believes HHS has a vital role to play in the global efforts to make the *Decade of Vaccines* vision a reality. The recommendations and supporting rationale are intended to raise awareness of ongoing HHS efforts in the context of broader global initiatives, to build political and public support around these activities, and to ensure that these efforts will enhance USG efforts to continue to move the global immunization agenda forward. In turn, this will help better communicate HHS's accomplishments and resource gaps to decision-makers and the public. The recommendations should serve as a potential roadmap for better coordination and tracking of HHS global immunization efforts. The continued participation of HHS in the six priority areas identified by NVAC will make certain that global immunizations remain at the forefront of HHS global health priorities.

1 # List of Abbreviations

Acronym	Title
ACIP	Advisory Committee on Immunization Practices
AEFI	Adverse Event Following Immunization
AES	Acute Encephalitis Syndrome
AFP	Acute Flaccid Paralysis
AMES	Acute Meningitis/Encephalitis Syndrome
ASH	Assistant Secretary for Health
AVAREF	African Vaccine Regulators Forum
AVI	Accelerated Vaccine Introduction Initiative
BARDA	HHS Biomedical Advanced Research and Development Authority
CBER	FDA Center for Biologics Evaluation and Research
CCL	Cold Chain and Logistics
CDC	U.S. Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
CRS	Congenital Rubella Syndrome
CTC	Controlled Temperature Chain
cVDPV	circulating Vaccine-Derived Polio Virus
DCVM	Developing Country Vaccine Manufacturers
DCVRN	Developing Country Vaccine Regulators Network
DTP	Diphtheria-Tetanus-Pertussis
DoD	Department of Defense
EOC	Emergency Operations Center
EPI	Expanded Programme on Immunization
FDA	U.S. Food and Drug Administration
FE(L)TP	Field Epidemiology and Laboratory Training Program
FIC	NIH Fogarty International Center
GACVS	Global Advisory Committee on Vaccine Safety
GAP	Global Action Plan for Pandemic Influenza Vaccines
GAVI	The GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization)

Acronym	Title
GCG	ICH Global Cooperation Group
GCP	Good Clinical Practices
GDP	Gross Domestic Product
GHS	Global Health Strategy
GID	CDC Global Immunizations Division
GISRS	Global Influenza Surveillance and Response System
GIVS	Global Immunization Vision and Strategy
GMP	Good Manufacturing Practices
GNI	Gross National Income
GOARN	Global Outbreak Alert and Response Network
GPEI	Global Polio Eradication Initiative
GVAP	Global Vaccine Action Plan
GVSI	Global Vaccine Safety Initiative
HHS	U.S. Department of Health and Human Services
Hib	*Haemophilus influenzae* Type b
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
IBD	Invasive Bacterial Disease
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iSCL	Immunization Supply Chain and Logistics Hub
IDSR	Integrated Disease Surveillance and Response
IFFIm	International Finance Facility for Immunization
IHR	International Health Regulation
IPV	Inactivated Polio Vaccine
ISO	CDC Immunization Safety Office
JEV	Japanese Encephalitis Virus
LMIC	Low- and Middle-Income Countries
MenA	Meningococcus Type A
MDG	Millennium Development Goals
MMR	Measles-Mumps-Rubella

Acronym	Title
MR	Measles-Rubella
MRI	Measles-Rubella Initiative
NGO	Non-Governmental Organization
NIC	National Influenza Centre
NIH	U.S. National Institutes for Health
NITAG	National Immunization Technical Advisory Group
NRA	National Regulatory Authority
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	U.S. National Vaccine Program Office
OGA	HHS Office of Global Affairs
OPV	Oral Polio Vaccine
PACTR	Pan African Clinical Trials Registry
PAHO	Pan-American Health Organization
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal Conjugate Vaccine
PDP	Product Development Partnership
PHS	U.S. Public Health Service
PMS	Post-Marketing Surveillance
R&D	Research and Development
RED/C	Reaching Every District/ Community
SAGE	Strategic Advisory Group of Experts
SIA	Supplementary Immunization Activities
SISB	CDC Strengthening Immunization Systems Branch
SIVAC	Supporting Independent Immunization and Vaccine Advisory Committees
SMART	Strategic Multi-Attribute Ranking Tool
STOP/ N-STOP	Stop Transmission of Polio/ National Stop Transmission of Polio
SQUID	CDC Strengthening Quality and Use of Immunization Data
TPP	Target Product Profiles
UMC	Uppsala Monitoring Center

Acronym	Title
VPD	Vaccine-Preventable Diseases
VPPAG	Vaccines Presentation and Packaging Advisory Group
WHA	World Health Assembly
WHO	World Health Organization
WPV	Wildtype Polio Virus
UNF	United Nation's Foundation
UNICEF	United Nations Children's Fund
USAID	U.S. Agency for International Development
USG	U.S. Government
VAERS	Vaccine Adverse Events Reporting System
VSD	U.S. Vaccine Safety Datalink

2

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Introduction

Global immunization programs strive to achieve high levels of disease prevention and equitable access to healthy communities. Immunizations are estimated to have saved 20 million lives over the past two decades. Yet, vaccine-preventable diseases continue to cause 1.9 million childhood deaths every year[1]. This translates to a child dying of a vaccine-preventable disease every 20 seconds.

During the Child Survival Call to Action summit hosted in June 2012, world leaders stated that unless global efforts were increased, the world would fail to reach the 2015 Millennium Development Goal of reducing childhood mortality by two-thirds of the levels recorded in 1990 (Millennium Development Goal #4)[2]. It was noted that accelerated strategies would need to include *"cost-effective, evidenced-based interventions and delivery strategies that have the largest potential for sustained impact"*[3]. Global commitment to strengthening immunization programs is paramount to reaching these goals.

The United States has been a leader in supporting global immunization efforts. U.S. investments in global vaccines and immunization infrastructure have been leveraged to improve the health and well-being of individuals through better access to healthcare systems, to protect against international and national public health threats, and to foster global health diplomacy. Protecting these assets and determining how to optimize the contributions of the U.S. toward achieving global health goals should remain a priority for the U.S. government.

Charge to the National Vaccine Advisory Committee

In February 2012, the Department of Health and Human Services (HHS) Assistant Secretary for Health (ASH) charged the National Vaccine Advisory Committee (NVAC) with:

- Reviewing the role of HHS in global immunization
- Reviewing the effects of global immunizations on global populations
- Reviewing the effects of global immunizations on U.S. populations
- Recommending how HHS can best continue to contribute, consistent with its newly established Global Health Strategy and Goal 5 of the National Vaccine Plan
- Recommending how to best communicate this information to decision makers and the general public to ensure continued sufficient resources for the global vaccination effort

The NVAC formed a Global Immunization Working Group consisting of experts in issues relevant to all aspects of the global immunization efforts to address this charge.

The NVAC's findings outline a number of global initiatives and global efforts towards improving the prevention and control of important infectious diseases through immunizations that require participation by the full range of global immunization stakeholders. However, this report is not intended to represent an exhaustive catalog of global immunization activities, but rather those activities that could be further strengthened through enhanced HHS efforts. It should also be noted that the U.S. global immunization efforts include a number of significant contributions made by other U.S. agencies that are not detailed here. These include efforts by the U.S. Agency for International Development (USAID), the U.S. Department of Defense (DoD), the State Department, and others. Though these efforts are not described in detail, the ongoing contributions by these U.S. agencies, especially USAID, in collaboration with HHS, are vital to achieving objectives for global health. Finally, while the NVAC's focus was specifically on providing input to strengthen HHS-led activities, these recommendations are also intended to inform, guide, and create new opportunities for coordination of global immunization efforts across the federal agencies and the full spectrum of immunization stakeholders.

Global Immunizations: High Impact, High returns

Global immunization is one of the best investments in public health. Immunization programs save the lives of approximately 2.5 million children every year[4]. In 2011, 83% of children worldwide were fully vaccinated with three doses of the diphtheria-tetanus-pertussis (DTP) vaccine and 84% were vaccinated with at least one dose of measles-containing vaccine[5]. Liu *et al* estimate that from 2000 - 2010 global campaigns against measles have contributed to an 18% reduction in overall childhood mortality (under five years)[1]. This incredible accomplishment is predicted to have averted a cumulative 12.7 million deaths[6,7]. The recent Global Burden of Disease Study indicated that accelerated measles control efforts led to an 80% reduction in measles-related mortality between 1990 (630,000 deaths) to 2010 (125,000 deaths)[8]. Others have presented more conservative estimates of a 71% reduction in measles-related deaths from 2000 (542,000 deaths) to 2011 (158,000 deaths) [9]. These achievements in global measles control have resulted in a lower risk of measles importations into the U.S., where measles has not been endemic for more than a decade.

Though routine immunization programs already have had an enormous impact on reducing child mortality, their potential is much greater[4]. A quarter of the 7.6 million annual deaths in children under five years of age are still due to vaccine preventable diseases[1]. Progress towards the Global Immunization Vision and Strategy (GIVS) (2006-2015) goal of 90% coverage for the third dose of DTP containing vaccines and single dose of measles containing vaccines is suboptimal, particularly among priority countries[10]. For example, it is estimated that 22.4 million children annually are still not being fully immunized with three doses of DTP (DTP3), according to recommendations[5].

In addition to strengthening access to routine immunizations through systems strengthening efforts, creating increased access to new and underutilized vaccines has the potential to greatly affect further reduction in childhood mortality. For example, vaccines targeting *Haemophilus influenzae* type b (Hib), pneumococcal disease, and rotavirus as part of a coordinated efforts that also target water, sanitation, and nutrition are expected to significantly reduce the global incidence of pneumonia and diarrhea, two of the leading causes of under-five mortality in children[1,11,12]. Modeling estimates predict 23 million future deaths could be averted over the next decade (2011-2020) if high global coverage can be achieved for both routine and new/under-utilized vaccines, underscoring the remarkable impact that improved, equitable access to immunizations could have on reducing mortality.

Table 1. Number of deaths averted by antigen and vaccination strategy in persons forecasted to be vaccinated between 2011-2020 in 73 GAVI eligible countries (compared to no vaccination)[a]

Antigen[b]	Strategy	Number of persons vaccinated	Number of future deaths averted
HepB	Routine[c]	585,467,590	4,851,930
Hib	Routine	544,375,979	1,395,024
HPV	Routine	34,734,805	525,869
Japanese encephalitis	Campaign	86,709,020	7,778
Japanese encephalitis	Routine[d]	137,837,848	57,178
Measles	Routine 1st dose	623,754,317	10,296,017
Measles	Routine 2nd dose	154,153,515	288,394
Measles	SIA[d,e]	808,840,938	2,860,093
MenA	Campaign	238,708,529	248,257
MenA	Routine	59,280,269	4,742
Rotavirus	Routine[d]	262,065,510	805,561
Rubella	Campaign[f]	587,376,493	404,959
S. pneumoniae	Routine	358,561,865	1,544,762
Yellow Fever	Routine	174,242,766	34,849
Total		4,656,109,444	23,325,413

[a] This table has been adapted from **Lee *et.al.*, 2013**[11]

[b] hepatitis B (HepB), *Haemophilus influenzae* type b (Hib), human papillomavirus (HPV), and *Neisseria meningitidis* serogroup A (MenA)

[c] Assumes no birth dose

[d] The impact of routine vaccination with Japanese encephalitis and *N. meningitidis* serogroup A was calculated as the incremental impact above one-time mass-vaccination campaigns. The impact of routine second-dose measles vaccination was calculated as the incremental impact above routine first-dose measles vaccination; the impact of measles SIAs was calculated as the incremental impact above routine first- and second-dose measles vaccination.

[e] Measles supplementary immunization activities (SIA) include catch-up (9 months to 14 years old) and follow-up (9 months up to 10 years old) campaigns.

[f] Because of the computationally intensive nature of the rubella model and time constraints, the number of congenital rubella syndrome deaths averted were calculated for only the 50 countries projected to introduce rubella vaccine with GAVI support; another 18 GAVI-eligible countries, primarily in Europe and the Americas, that have already introduced rubella vaccine with other funding, were not included.

In addition to disease prevention, immunization programs provide broad economic and societal benefits[13]. Immunizations with seven routine vaccines* in one U.S. birth cohort were estimated to result in a savings of US $10 billion in direct costs and US $43 billion in societal costs (1995-2001)[14]. From another perspective, every dollar spent during this time period on childhood immunizations in the U.S.

* DTaP, Td, Hib, IPV, MMR, HB, and varicella

resulted in savings of US $5 in direct costs and US $11 in societal costs[14]. On a global scale, the economic impact of investments to reduce the mortality caused by vaccine-preventable diseases is also significant. Bloom *et al*. estimated that by 2020, the benefits of investments made by the Global Alliance for Vaccines and Immunizations (the GAVI Alliance) could yield an internal rate of return up to 18%[15]. This does not include other benefits such as medical costs averted, reduced suffering, or other societal benefits.

Diseases such as paralytic poliomyelitis, congenital rubella syndrome, or Japanese encephalitis can result in permanent disabilities that have lasting effects on a child's quality of life and their ability to contribute to and benefit from a global economy[15]. For example, in the U.S. the lifetime costs of caring for a severely disabled survivor of the 1964 U.S. rubella epidemic are estimated at $159,530 per year (CDC personal communication). In contrast, the cost to fully vaccinate a child in a developing country with two doses of the measles-rubella combination vaccine (MR) is approximately US$1.00 (2012 projected weighted average reported by UNICEF for MR 10-dose vial was US$ 0.513 per dose, excluding delivery costs)[16].

Part of the challenge of measuring the impact of vaccines is that when they work, healthy people remain healthy. Though more difficult to quantify, childhood vaccinations also contribute to societal benefits such as improved cognitive function, greater health equity, productivity gained, and overall population health through herd immunity[15,17,18].

Investments in immunization programs also benefit other global programs, as immunizations are often combined with the delivery of other health services[6,19–21]. Immunizations are only one component of a comprehensive prevention package and programs should be implemented in such a way that creates synergy with other health intervention activities. During the early implementation of the Expanded Programme on Immunizations (EPI) in 1976, the Director General of the World Health Assembly wrote that the "*EPI should preferably be part of UNICEF's 'social package' of primary health care activities but only exceptionally develop as a programme per se*"[22]. Immunization activities (both routine and supplemental) create contact opportunities to provide other critical preventive health services such as the administration of de-worming medications, vitamin A supplements, insecticide-treated bed nets, additional vaccines, and other health services targeting women and the impoverished[6,19,20,23–26].

The ultimate expression of vaccination is the complete eradication of a vaccine preventable disease. Eradication or elimination is not always technically feasible or cost-effective for all vaccine-preventable diseases. However, when achievable, eradication has proven to have significant cost-benefits. It is estimated that the total U.S. investments in the smallpox eradication campaign are returned every 26 days[27]. Others estimate that the incremental global net benefits of the Global Polio Eradication Initiative (1988-2035) is approximately US$40-50 billion, with most savings occurring in developing nations[28]. Again, this does not include projected estimates of medical costs averted. In a retrospective analysis of the total cost benefits of polio vaccination efforts in the U.S. from 1955-2015, Thompson and Tebbens calculated that the U.S. alone will benefit with cost-savings of ~US$180 billion (2002 US$) based on the number of deaths averted, number of paralytic polio cases averted, and total savings from treatment costs averted[29]. Moreover, savings from these efforts can provide the potential opportunity to use funds that had been dedicated to disease control efforts for broader purposes such as strengthening health systems.

The Cost of Measles Outbreak Response in the US

Outbreak response to imported vaccine-preventable diseases is both labor and resource intensive, requiring both state and federal resources. Recent U.S. measles outbreaks have incurred significant costs despite their relatively small size[425].

- In Iowa, a student infected with measles while traveling internationally, subsequently led to two additional measles cases upon return to the U.S. Public health officials had to track >1,000 contacts including airplane passengers and local residents. The response involved >2,500 hours of personnel time and costs to public sector exceeded $140,000. This did not including resources used outside of the state public health infrastructure including collaborations with the airlines, the CDC and other containment efforts[426].
- A health-care associated measles outbreak related to an imported case occurred in an Arizona hospital with 14 confirmed cases of measles. The outbreak required follow up on the vaccination status of 14,844 health care workers in seven hospitals and the emergency vaccination of 4,500 health care workers with unknown immunity status. The cost of this response in two hospitals with seven cases was estimated to be ~$800,000[427].
- An imported measles case in a refugee child was identified shortly after the child's family was resettled in Louisville, KY. Though only the single index case occurred, the outbreak investigation and public health response activities were estimated to cost the state $19,000 - $30,000. This did not include any of the costs incurred at the federal level[252].

Response efforts detract time and resources from the other vital activities public health departments engage in that guard national health. Reducing the global burden of vaccine preventable diseases is more than providing humanitarian aid for developing countries- it is also necessary for protecting our public health systems in the U.S.

Vaccine-Preventable Diseases Remain a Priority for the U.S.

Global immunization efforts are mutually beneficial for the U.S. population as well as the global community. When global immunization programs in other countries begin to weaken, disease incidence increases creating vulnerabilities for the U.S. population from disease importations, especially for those who are too young to be vaccinated or who are immunocompromised. Moreover, the public health resources and tax payer dollars required to respond to and contain vaccine preventable disease outbreaks are substantial. The U.S. celebrated the elimination of

indigenous measles transmission in 2000. However, in 2011, the U.S. experienced 220 measles cases resulting from 17 outbreaks across 31 states because of importations of measles viruses from other countries[30]. This was the highest number of measles cases reported in the U.S. in 15 years. It was determined that 18 cases occurred in children too young to be vaccinated. Seventy-two cases were importations from other countries (52 of these cases occurred in U.S. residents returning from abroad and 20 occurred in individuals visiting the U.S.). The remaining cases were due to presumed importations.

U.S. investments in global immunizations ensure safer, healthier environments for U.S. citizens abroad, while preventing the consequences of outbreaks due to vaccine-preventable disease at home. Orenstein, 2012 wrote *"[r]egarding vaccine-preventable diseases, the best defense for the United States is a good offense in reducing, eliminating, or eradicating these diseases in other countries, which are reservoirs for the infectious agents"*[31].

Immunization Efforts are a Shared Responsibility

Disease transmission rarely respects political boundaries and because of the availability of modern forms of travel, often supersedes geographical barriers. Disease control must therefore be a shared responsibility[32]. The global immunization enterprise comprises a wide range of stakeholders including developing and donor countries, multilateral organizations, development agencies, philanthropic organizations, academics, vaccine manufacturers, civil societies, healthcare workers, advocacy groups and the private sector. Routine immunization programs may be wholly or partially funded by the countries themselves, and the majority of World Health Organization (WHO) member states now include specific line items in their national budgets for the purchase of vaccines[33].

Global collaborations and public-private partnerships focused on either specific pathogen-driven initiatives or broader immunization-related issues are also critical to garnering the political support, community involvement, and the scientific, technical, and economic resources needed to achieve targeted disease control efforts. Coordinated efforts such as the Global Polio Eradication Initiative[34], the Measles/Rubella Elimination Initiative[25], the Meningitis Vaccine Project[35], the Maternal and Neonatal Tetanus Elimination Initiative[36], the GAVI Alliance[37], and others are just some examples of the global community's joint commitment to overcoming vaccine-preventable diseases.

The Roots of the Expanded Programme on Immunizations

The triumph of smallpox eradication in 1980 is often viewed as a transcendent achievement in public health. Richard Preston wrote "*It was one of the noblest and best things that we have ever done as a species*"[428]. The smallpox eradication campaign demonstrated that universal access to a vaccine was attainable and that a vaccine-preventable disease could be vanquished when global resources and political will were galvanized towards common public health goals.

Countries saw an opportunity to leverage the momentum gained by the smallpox campaign's unprecedented success to create a broader platform for delivering other life-saving vaccines and health interventions[429]. In 1974 the World Health Assembly (WHA) voted to create the Expanded Programme on Immunizations (EPI)[22]. The EPI resolution called on all member states "to establish and maintain immunization and surveillance programs against vaccine preventable diseases with the goal of reducing overall morbidity and mortality"[430].

The WHA noted that success would depend on the full participation of member states in designing immunization programs that were suitable to the needs and capabilities of their countries[431]. In turn, the World Health Organization (WHO) committed to collaborating with countries to provide the technical and operational support to implement programs; to provide high quality, safe vaccines; to create a reliable supply system; and to promote research and development activities.

Finally, UNICEF was granted responsibility for the procurement of EPI-recommended vaccines to ensure the equitable distribution of vaccines for all regions and to incorporate vaccinations into other health care packages[431]. Later PAHO would establish the Revolving Fund to finance the purchasing of vaccines and vaccine supplies for the Region of the Americas.

In 2005, the WHO and the United Nations Children's Fund (UNICEF) presented the 2006-2015 Global Immunization Vision and Strategy (GIVS) to the 58th World Health Assembly as a 10-year strategic guidance document for further improving immunization access. The GIVS emphasizes making immunization programs a national priority, not only because equitable and sustainable access to immunizations saves lives, but also because immunization programs can be used as a platform for building better health delivery systems[38].

The shared momentum for global immunization efforts continues to build fueled in large part by the Decade of Vaccines collaboration launched in 2010[39]. Following its endorsement by all member states at the 64th World Health Assembly, the Decade of Vaccines represents a pledge from all immunization stakeholders to commit to realizing "*a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases*"[39].

A Global Vaccine Action Plan (GVAP) was developed by the Decade of Vaccines leadership[†] in consultation with over 1,100 stakeholders from over 140 countries and 290 organizations. Approved by the 194 countries of the 65th World Health Assembly in May 2012, the GVAP builds on the Global Immunization Vision and Strategy (GIVS) by evaluating the lessons learned from the first few years of GIVS implementation[40].

The GVAP lays out a roadmap for bringing the full benefits of immunizations to all people by 2020[41]. It stresses six key principles for success that include country ownership, shared responsibility and partnership, equitable access to immunizations, integration of immunizations into health systems, financial sustainability, and innovation[41].

Overcoming Key Challenges to Global Immunization Programs

Numerous challenges can weaken routine immunization systems. Difficult-to-reach populations may face barriers to providing equitable access to immunization services, leading to a range in coverage rates between and within countries. Mass vaccination campaigns following outbreaks can greatly stress limited resources, such as the number of available trained healthcare workers needed to carry out routine programs. Moreover, poor program management can create difficulties in monitoring and evaluating programs, further complicating planning efforts[42,43].

Countries with weak routine systems can face further challenges when trying to incorporate new or underutilized vaccines into their programs. Insufficient surveillance capabilities may underestimate the disease burden within a region, leading decision-makers to question the need for or cost-effectiveness of a new vaccine resulting in unnecessarily prolonged delays in introduction[44]. Some countries may need additional technical and financial support to accommodate additional vaccines into their immunization programs to overcome barriers such as cost or a lack of logistical capacity to safely deliver vaccines including a reliable cold-chain, a vaccine safety monitoring system, and a trained workforce[45]

[†] The Decade of Vaccines leadership includes the WHO, UNICEF, the Bill & Melinda Gates Foundation, the GAVI Alliance, the U.S. National Institute of Allergy and Infectious Diseases, and the African Leaders Malaria Alliance

The GAVI Alliance was formed in 2000 as a mechanism for addressing resource constraints for vaccine financing and systems strengthening in the poorest countries. The GAVI Alliance represents a global partnership between a diverse representation of public and private entities whose combined resources provide financial support to eligible, low-income countries. GAVI's mission is to save children's lives and improve peoples' health by increasing access to immunization in poor countries. The Alliance has four strategic goals; 1) accelerating uptake and use of new and underused vaccines, 2) contributing to strengthening the capacity of integrated health systems to deliver immunization, 3) increasing the predictability of global and national financing, and 4) shaping vaccine markets. [37].

New Tools for Immunization Financing

Support from the GAVI Alliance comes from a number of funding mechanisms including direct donor support, monies from the sale of "vaccine bonds" through the International Finance Facility for Immunization (IFFIm), and advanced market commitments from donors.

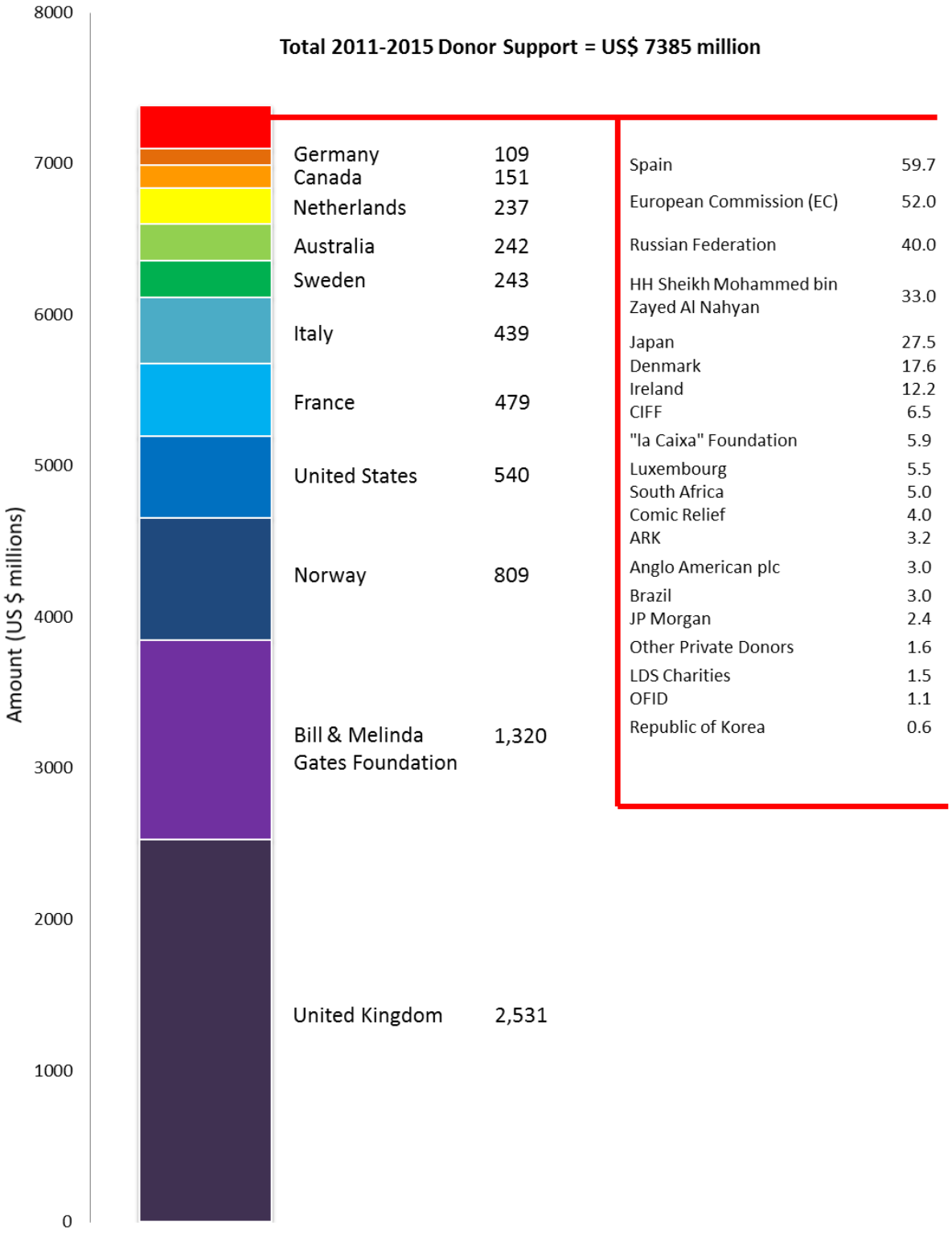
The IFFIm functions by issuing bonds from legally-binding, long-term donor pledges, which are sold on the international capital markets. The proceeds from the sale of these bonds becomes a cash resource available immediately to fund GAVI activities[46].

Advanced market commitments establish a guaranteed market for vaccines tailored to meet the specific public health needs of developing countries [4]. Donor pledges establish a fixed price for a vaccine once it has been developed and manufactured. Once donor commitments are spent, companies are obligated to offer accessible vaccine pricing, helping introduce new vaccines in resource poor countries.

Eligible countries are required to have a per capita gross national income (GNI) of ≤ US$1,550 and must demonstrate that they are able to achieve at least 70% coverage for three doses of the DTP vaccine prior to the introduction of new vaccines[37]. Financial support is based on a sliding scale, and countries are expected to bear increasing shares of the vaccine costs as their GNI per capita increases, allowing for a sustainable and fair funding mechanism. Co-financing reinforces country-ownership of immunization programs, and upholds a country's commitment to prioritize immunizations as an essential component of their broader health delivery services. In addition, countries must submit a costed, comprehensive multi-year plan for immunization, to ensure that their programs are sustainable over time[33].

Currently, over 26 donors (including government, non-profit, and private contributions) have jointly pledged US $7.326 billion to the GAVI Alliance between 2011- 2015 to help low-income countries better provide immunization services to all people (Fig.1). Activities funded by the GAVI Alliance are estimated to have expanded immunization access to over 325 million children[46]. However, middle income countries and those that do not qualify for GAVI support still face financial barriers to introducing new vaccines as they become available[18].

Figure 1. 2011 – 2015 GAVI Donors Contributed or Pledged Funding



282

The U.S. Commitment to Global Immunization Efforts

Even in the current economic climate, maintaining or increasing U.S. funding for global immunization programs and global health is broadly supported by the majority of Americans. In 2012, the Kaiser Family Foundation reported on a survey assessing the American public's opinion on the role of the U.S. in improving the health of people in developing countries[47]. A striking 58% of participants stated that improving children's health, including vaccinations, should be a top priority for U.S. assistance in developing countries. An additional 28% stated that it should be considered important but not a top priority[47].

The American people's support for global immunization programs is reflected in the U.S. government's financial commitments during the last decade. In the ten year period spanning 2001-2011, the U.S. financial contributions to the GAVI Alliance totaled US $736 million, made through USAID, exclusively for the procurement of vaccines. In recent years, the USG has shown strong commitment to global health initiatives including disease specific goals such as worldwide polio eradication. During fiscal years 2009 through 2012, the U.S. contributed a total of US$541.3 million towards polio eradication, and funded US$192.0 million for work to control other vaccine preventable diseases including measles (CDC Budget Justifications from 2011 and 2013). Additionally, these numbers do not reflect the resources dedicated to providing technical assistance, vaccine research and development efforts, and other activities that benefit global populations by creating and enhancing access to vaccines.

Table 2. USG Contributions to Global Polio Eradication Efforts (2009-2012)

Year	USAID	Economic Support Fund Account (State Department)	CDC (HHS)	**TOTAL**
2009	$20.7 million	---	$101.5 million	**$133.5 million**
2010	$29.0 million	$3.0 million	$101.8 million	**$136.1 million**
2011	$32.9 million	---	$101.6 million	**$133.9 million**
2012	$35.0 million	$4.5 million	$111.3 million	**$150.9 million**
TOTAL	$131.6 million	$6.5 million	$416.2 million	**$554.4 million**

Global Health and the Role of the U.S. Department of Health and Human Services

The U.S. government is committed to creating a safer and healthier world by reducing the global burden of vaccine-preventable diseases, improving equitable access to health care services for all people, and achieving health security and health diplomacy through international collaborations. A number of U.S.

agencies including HHS, USAID, DoD, and the State Department provide specific support for these objectives through pro-vaccination policies, programmatic activities, collaborations, and financial assistance. Although the specific global health mandates of each agency may differ, their collective actions bolster the capabilities of the entire global immunization enterprise.

Global health prevention and disease control, particularly through safe and effective vaccination, are stated priority goals of HHS, as evidenced in both the HHS Global Health Strategy and the 2010 National Vaccine Plan[48–50]. The HHS Global Health Strategy underscores the role of HHS as a leader in global health and highlights HHS's commitment to a more systematic approach to global health issues. The Strategy's ten objectives describe a spectrum of health capacity-building efforts that directly impact global immunization efforts. The 2010 National Vaccine Plan (NVP), put forth by the HHS National Vaccine Program Office, outlines a 10-year strategic vision for coordinating national immunization efforts both within and outside of the federal government[48]. The NVP specifically highlights "supporting the global introduction and availability of new and underutilized vaccines to prevent diseases of public health importance" as a priority for implementation to create an "*umbrella of protection*" for public health within the U.S.

HHS consists of 11 agencies and 18 staff offices that serve to protect the well-being of Americans both here and abroad by supporting advances in science, medicine, public health, and the delivery of social services. This includes strong support of global initiatives, as well as establishing national objectives for raising the standards for global public health. In particular, agencies and offices under HHS including the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the National Vaccine Program Office, and the Office of Global Affairs demonstrate core competencies that will be necessary to realize the full benefits of the "decade of vaccines". These activities include, but are not limited to, expanding scientific research capacity, forwarding innovations in vaccine development, manufacturing and licensure, optimizing disease control efforts, building public demand for vaccines, and establishing a strong evidence base to support the decision-making process regarding the introduction of new vaccines.

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NVAC Analysis and Recommendations:

The NVAC recognizes that the HHS activities described throughout this report are critical to achieving national and global goals for strengthening immunization programs and reducing morbidity and mortality due to vaccine preventable diseases. Building political and public support around these activities will be necessary to ensure that these efforts will continue to move the global immunization agenda forward. This includes continued financial investments in a range of activities associated with global immunizations. As the charge to the NVAC by the Assistant Secretary for Health was to focus on HHS activities, this analysis will concentrate on those activities and is not intended to represent a comprehensive description of all USG efforts.

1. Tackling Time-Limited Opportunities to Complete Disease Eradication and Elimination Goals

NVAC Recommendations:

1.1 The Assistant Secretary for Health (ASH) should communicate to key audiences (including Capitol Hill and the general public) the urgency of completing global goals for polio eradication and advancing global measles mortality reduction goals and regional goals for measles/rubella elimination. The ASH should engage these key audiences via briefings, events, and other educational activities.

1.1.1 The ASH should emphasize that polio eradication efforts and measles mortality reduction and regional elimination efforts should complement and strengthen routine immunization systems.

1.1.2 The ASH should emphasize that failure to complete polio eradication goals or to advance goals for measles mortality reduction and regional goals for measles/rubella elimination may threaten the health of US populations due to importations of these diseases from endemic areas.

1.1.3 The ASH should emphasize that political and public support is fundamental to achieving polio eradication and advancing global goals for measles mortality reduction and regional goals for measles/rubella elimination. Achieving these goals would equal a monumental public health and humanitarian accomplishment for the entire global community and if done appropriately, will potentially strengthen support for routine immunization goals.

As the arm of HHS dedicated to operationalizing disease prevention and control strategies, CDC has provided unparalleled scientific and technical leadership in combating vaccine preventable diseases within the U.S. and worldwide. CDC has been, and continues to be, a pivotal player in a number of disease elimination and eradication efforts including the Smallpox Eradication Campaign, the Global Polio Eradication Initiative (GPEI), the Measles/Rubella Initiative (MRI), and the Maternal and Neonatal Tetanus Elimination Initiative.

In 2010, global immunization initiatives, including polio eradication, were declared one of CDC's 10 "winnable battles" as a way to spotlight the issues and draw up greater support from partner organizations and public leaders. Winnable battles represent public health priorities that have a large-scale impact on health with known, effective strategies for addressing them[51]. As part of the "battle plan" for achieving global immunization goals, the CDC's 2011-2015 Global Immunization Strategic Framework describes six overarching goals that harmonize CDC activities with international immunization priorities. The framework ensures progress towards these goals by setting metrics on specific objectives to be tracked over time[50]. Included in these objectives are 2015 targets to certify polio eradication and to reduce estimated global measles mortality by 95% or greater compared to 2000 levels. The Decade of Vaccines Global Vaccine Action Plan (GVAP) states that measures of success for the Decade of Vaccines initiative will include achieving certification of global polio eradication and measles/rubella elimination in at least five WHO regions by 2020[41].

These goals are achievable. In fact, the world is closer than ever before to realizing these goals. However, despite the impressive progress that has been made on both of these fronts, the headway gained over the past three decades towards polio eradication and measles mortality reduction are fragile. As long as these diseases persist, all countries will remain vulnerable to resurgence and disrupting the transmission of the disease will require ongoing global action. Every new birth cohort introduces susceptible individuals into the population, and weakening of efforts to sustain high vaccine coverage levels throughout a population will result in outbreaks, threatening regions that have already made significant progress against these diseases[52,53]. For example, measles transmission can be maintained even when >90% of the population is protected[54].

The Global Polio Eradication Initiative

In the 1980s, an estimated 350,000 cases of paralytic polio occurred annually in 125 endemic countries around the world[55]. More than 200,000 of these cases occurred in India, translating to approximately one case every three minutes[56,57]. In 1988, the WHA unveiled a vision for polio eradication with a target date of 2000, prompting the creation of the Global Polio Eradication Initiative (GPEI), a public-private partnership launched by the WHO, Rotary International, UNICEF, CDC, and led by national governments[55]. By 2002, the efforts of the GPEI had reduced the global incidence of polio worldwide by 99% and only seven countries remained endemic[58,59]. Polio had been eliminated in the Americas (1994), the Western Pacific (2000), and Europe (2002)[57]. However, momentum was difficult to sustain over time and the prolonged eradication efforts began to exhaust the public health community.

Between 2001 and 2011, the reduction in polio cases plateaued[60,61]. Barriers in the remaining endemic countries including weak immunization programs, poor management and accountability, suboptimal quality of implementation strategies, misconceptions about the safety of the vaccine (resulting in a widespread loss of public demand for vaccination), political turmoil, and armed conflict caused significant gaps in vaccine coverage, and in some cases, complete disruption of polio campaign activities[62–69]. This led to exportation of polio cases from endemic countries into polio-free countries causing 59 polio outbreaks in 39 countries that were previously deemed polio-free over the past decade[60].

In 2002, countries in the European region began to experience complacency in maintaining high vaccination coverage rates. The national polio vaccination coverage rates in the country of Tajikistan fell from 86% in 2000 to 76% in 2006[70]. As a consequence, in 2010 an imported case of wild-type polio virus from India led to 458 cases of laboratory-confirmed polio in Tajikistan[71]. Factors leading to the rapid spread of the virus included poor vaccine coverage, inadequate surveillance, and a resource-limited health system[71]. Subsequent importations from Tajikistan spread the virus to three other polio-free countries including Russia, Turkmenistan, and Kazakhstan. In total, the outbreak resulted in 476 confirmed cases, and 26 deaths[71]. Supplementary immunization activities were conducted in all affected countries and the outbreak in the region was contained within six months.

In four countries in the African region (Angola, Chad, DR Congo, and Sudan), imported polio outbreaks led to re-established transmission, defined as previously polio-free countries in which reintroduction of poliovirus led to sustained transmission lasting >12 months. The consequences were significant; more than 1,500 children were left paralyzed and outbreak response efforts cost the global community more than US$500 million[59].

Public Support of Immunizations

The global vaccination effort ultimately depends on millions of families around the world demanding access to immunizations to protect their children from disease.

In China, an outbreak of polio in 2011 prompted the swift vaccination of 4.5 million children and young adults in the span of only five weeks [432]. When parents in clinics were asked why they went through so much effort and walked so far to get to the clinics, a mother responded:

You are a mother. How could you look your child in the eyes if you are not giving them the best chance to be healthy and avoid being sick with a virus that causes our children to be disfigured and limp? We cannot do that to our families.[432]

The spread of polioviruses and re-establishment of polio transmission in countries that had been deemed polio-free serve as a cautionary tale for what can happen when polio is not eradicated from all countries. The risk of exportation of polioviruses from endemic countries has elicited calls for substantially enhancing current efforts and strategies from some, including the GPEI Independent Monitoring Board which recommends that WHO member states require those traveling from a polio-endemic country to other countries to present certified documentation of vaccination to reduce the spread to polio-free countries[72]. Their report states "*no country should allow a citizen from any endemic polio state to cross their border without a valid vaccination certificate",* underscoring the significance of this threat to eradication goals[72]. In alignment with this, the WHO's International Travel and Health, 2012 edition recommends the full polio vaccination of travelers and indicates that some polio-free countries already require travelers from countries or areas reporting wild polioviruses to show certification that they have been immunized against polio in order to obtain an entry visa[73].

Although earlier goals to interrupt wild poliovirus transmission by 2012[74] were not met, there has been substantial progress in the past few years. Polio cases have dropped from 1352 cases (2010) to 650 cases (2011) and then to 223 cases (2012)[34]. Circulation of naturally occurring wildtype poliovirus type-2 has not been documented since 1999 and as of July 2013, no cases of wildtype poliovirus type-3 have been recorded for 2013. The GPEI estimates that it has administered more than 10 billion doses of oral polio vaccine (OPV) to 2.5 billion children world-wide, preventing more than 10 million cases of paralytic polio[75].

As the number of polio cases dwindles, countries will need to maintain high-quality surveillance efforts for the rapid detection and investigation of all acute onset flaccid paralysis cases. Moreover, environmental sampling and virologic characterization of stool samples will be important for detecting ongoing silent (asymptomatic or non-paralytic illnesses) transmission of polioviruses in communities. Laboratory networks will also need to be able to recognize and diagnose polio cases caused by circulating vaccine-derived polioviruses (cVDPV, vaccine viruses which through transmission and mutation have acquired the neurovirulence characteristics of wild polioviruses) from continued use of live-attenuated OPV. Importations of cVDPVs can also threaten polio-free communities where lower vaccination coverage is no longer at levels high enough to ensure herd immunity[76–78].To this end, experts now support the administration of at least one dose of the inactivated poliovirus vaccine (IPV) and the transition from the use of trivalent OPV (containing poliovirus types -1, -2, and -3) to bivalent OPV (containing poliovirus types -1 and -3) to mitigate the risk of continued cVDPV-type 2 circulation[79].

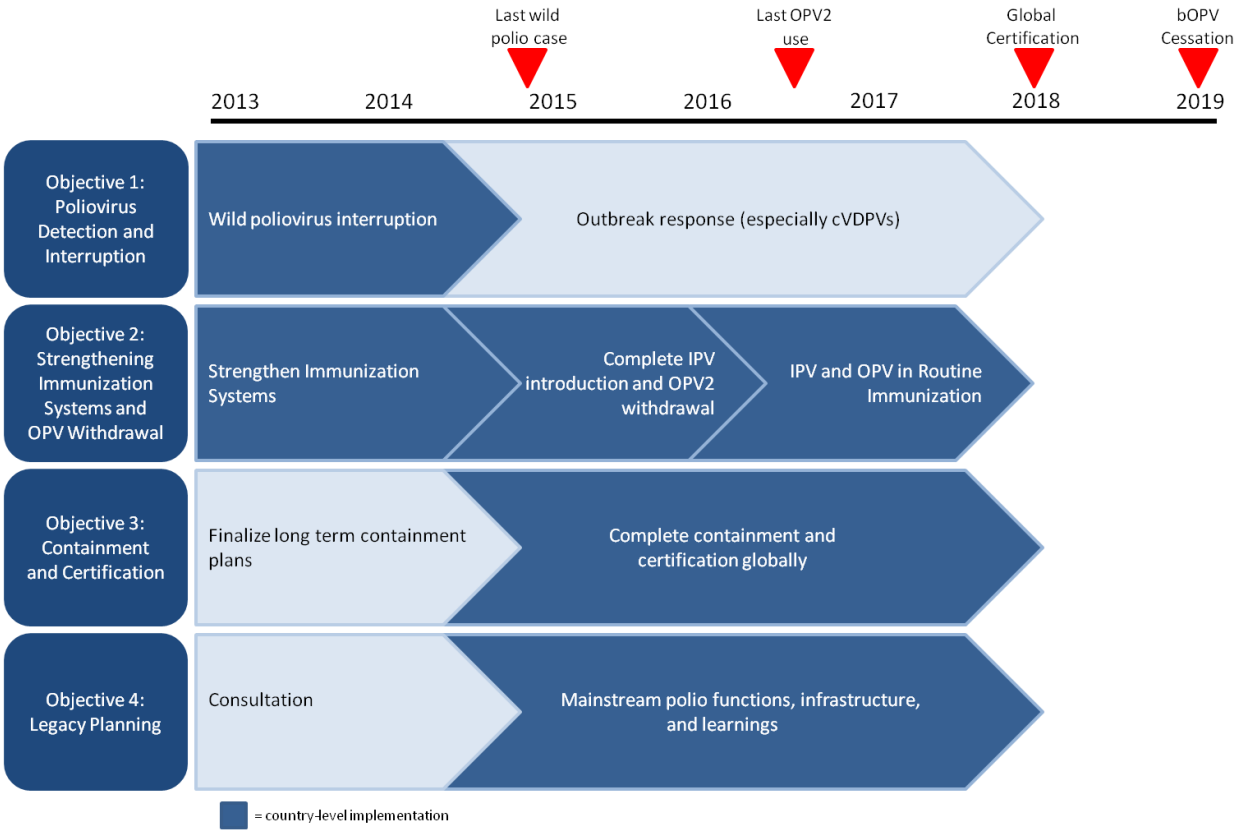
In order to guide accelerated efforts to achieve polio eradication, the CDC activated its Emergency Operations Center (EOC) on 2 December 2011 to respond to polio eradication as a global public health emergency. This has allowed the CDC to scale up partnership efforts including expanding technical assistance for vaccination and surveillance activities, improving program management and accountability, and strengthening immunization infrastructure to support the polio response. Since its activation, over 400 CDC personnel, both within the EOC and in the field, have contributed to the analysis, validation, and exchange of critical information to increase the program's situational awareness and enhance program support[80]. Similarly, the WHO's executive board declared polio eradication efforts a global programmatic emergency in January 2012, followed by the release of the 2012-2013 Global Polio Emergency Action Plan , which laid out specific efforts focused on overcoming the significant challenges posed by the last three endemic countries: Nigeria, Pakistan, and Afghanistan[81].

In April 2013, the GPEI introduced the 2013-2018 Polio Eradication and Endgame Strategy ("the Endgame Strategy") at the 2013 Global Vaccine Summit in Abu Dhabi, Dubai. Building off the momentum gained from the country-specific activities implemented in the 2012-2013 Emergency Action Plan, the Endgame Strategy was developed by the GPEI through extensive consultation with a number of stakeholders including the national health authorities in countries most affected by poliomyelitis.

As it states, the Endgame Strategy "*…accounts for the parallel pursuit of wild poliovirus eradication and cVDPV elimination, while planning for the backbone of the polio efforts to be used for delivering other health services to the world's most vulnerable children*"[75]. It advocates that strong, reliable routine immunization systems will be central to the GPEI's success and that sustaining routine systems will continue to benefit from GPEI investments long after the polio eradication has been achieved. Furthermore, the Endgame Strategy includes a comprehensive cost analysis for completing the objectives within the strategy, the responsible parties for ensuring oversight of goals and activities, a description of possible risks to completing goals and milestones, steps that will be taken to mitigate those risks, and a set of contingency options to minimize potential roadblocks[75,82].

The Endgame Strategy includes a comprehensive description of the GPEI's four objectives for achieving polio eradication within the six-year 2013-2018 timeframe and provides a new strategic focus based on the evaluation of previous program weaknesses and lessons learned[75]. Major milestones outlined in the Endgame strategy include 1) stopping all WPV transmission by the end of 2014 and stopping new outbreaks of cVDPV outbreaks within 120 days of an index case; 2) achieving at least a 10% year on year increase in DTP3 coverage in the worst performing districts in focus countries from 2014 to demonstrate routine immunization system strengthening activities; 3) introducing at least one dose of IPV in all OPV-using countries in 2015 and the withdrawal of OPV-2 globally in 2016; 4) establishing a comprehensive legacy plan by the end of 2015; and 5) certifying eradication and containing all facility-based wild polioviruses by the end of 2018[75] (Fig. 2 adapted from[75]).

Figure 2. Parallel Objectives of the Polio Eradication and Endgame Strategic Plan



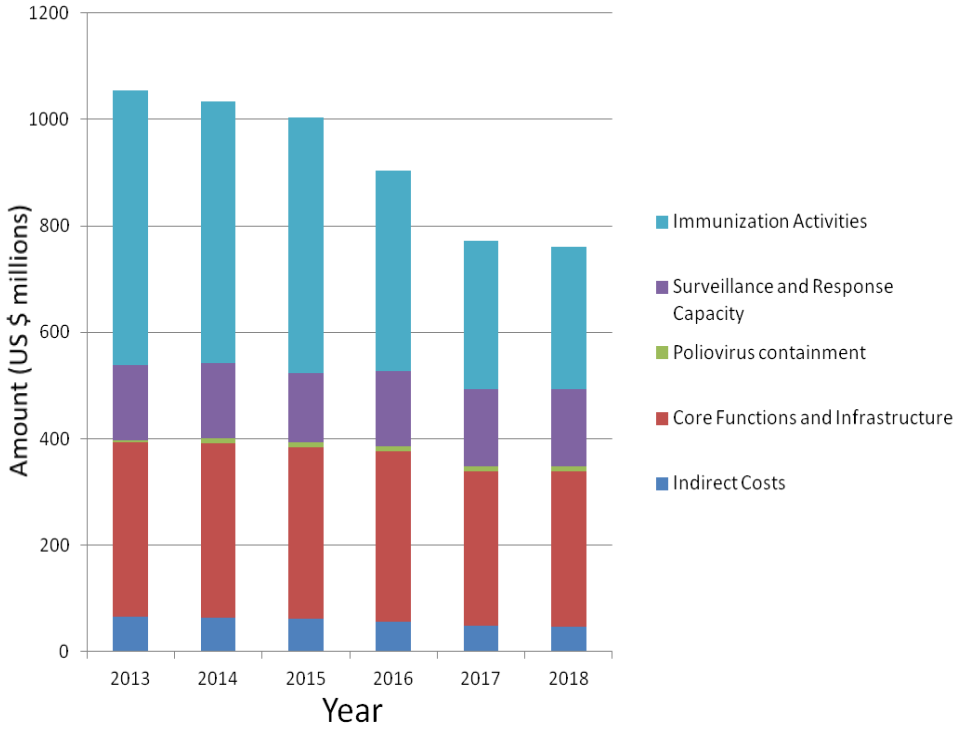
Notably, the Endgame Strategy calls for all countries to include administration of at least one dose of IPV into their routine immunization programs by 2015 in preparation for the withdrawal of trivalent OPV and the switch to bivalent OPV[79]. However, polio endemic countries and other countries at increased risk of polio re-introduction correlate with regions that persistently report high numbers of un- and under-vaccinated children[5]. This underscores the barriers that weak immunization systems pose to completing polio eradication goals. To address these challenges, the Endgame strategy indicates that activities to strengthen the overall immunization systems will be given the same importance and urgency as campaign activities. In support of this, the GPEI will devote at least 50% of the time of polio-funded personnel to activities that have a measurable impact on strengthening immunization systems and health services. Moreover, legacy planning (objective 4) will include the development of a framework to ensure the capabilities and infrastructure created by the GPEI will serve as platform to continue to build and strengthen global immunization systems as a whole (including trained public health workers, surveillance and laboratory capacity, response and containment functions, and tools for immunization program planning and monitoring)[75].

Finally, expert scientific and technical assistance is required to ensure that the polio endgame strategies fulfill the promise of stamping out polio forever. In April 2013, more than 450 scientific and technical experts from over 80 countries signed a scientific declaration on polio eradication voicing their "conviction that the eradication of polio is an urgent and achievable global health priority"[83]. The scientific declaration endorses the Polio Eradication and Endgame Strategy and urges all stakeholders to commit the financial and programmatic efforts required to complete these goals, as outlined in the Endgame Strategy[84].

Risks to Completing Polio Eradication

One of the greatest obstacles that continue to threaten the completion of polio eradication goals is insufficient funding to carry out immunization campaigns and program activities. The GPEI estimates that the 2013-2018 Polio Eradication and Endgame Strategy will require a total budget of US$ 5.5 billion, with costs peaking at US$1 billion in 2013 and declining annually to US$ 760 million in 2018 (Fig. 3 adapted from[82]). Currently, the GPEI faces a 2013-2018 budget shortfall of US $2 billion necessary for the continuation of critical supplementary immunization activities and efforts to strengthen existing vaccination programs. This shortfall assumes that donors are able to maintain their current levels of US$ 3.1 billion[82,85,86].

Figure 3. 2013-2018 GPEI Endgame Strategy Budget Plan by Category



The majority of the projected GPEI budget is dedicated to immunization activities - both OPV campaigns and incorporating IPV into routine immunization systems[82]. The breakdown of these costs are detailed in the Endgame Strategy companion document *Key Elements of the Financial Resource Requirements 2013-2018*[82].

Budget shortfalls in 2012 led to the cancellation and scaling back of polio campaign activities in 24 high-risk polio-free countries[81]. Analysis conducted by Thompson and Tebbens indicated that if GPEI efforts are abandoned and countries with high risk factors resort to low polio control efforts[‡] due to perceived costs-savings, the number of polio cases could undergo a resurgence, resulting in three million polio cases over a 20 year time frame (or 200,000 cases per year)[87].

On 27 May 2013, the World Health Assembly endorsed the new 2013-2018 Polio Eradication and Endgame Strategic Plan and urged for its full implementation and financing. Delegates acknowledged the progress achieved in the past year to reduce polio incidence to historical lows, thanks to actions of Member States that prioritized program activities by placing polio eradication on an emergency footing.

[‡] Defined in the report by Thompson and Tebbens, 2007 as polio immunizations solely as part of routine systems with no additional funding for supplemental immunization activities, outbreak response, or active surveillance for acute flaccid paralysis

The Measles/Rubella Initiative (MRI)

In 2000, the number of reported measles cases worldwide were estimated to number greater than 850,000 and an estimated 542,000 deaths were reported for that year[9], ranking measles the 19th leading cause of death worldwide . The Measles Initiative was founded in 2001 as a partnership between the WHO, UNICEF, CDC, the American Red Cross , and UNF to work with national governments, global and regional leaders, and donor organizations to financially and technically support accelerated measles control activities[88]. That same year, the Measles Initiative partnered with 19 African countries to implement measles control strategies. Within two years, the Initiative had successfully vaccinated more than 82.1 million children, and had reduced the number of measles-related deaths in the African region by 20%[89]. By 2010, the Measles Initiative had invested US $875 million in donor funds for measles control activities that have supported the vaccination of over one billion children in more than 80 countries[88]. Moreover, accelerated measles control efforts have led to a decrease in measles-related deaths by 71% between 2000 and 2011[9].

Congenital rubella syndrome (CRS) is one of the leading causes of preventable congenital birth defects worldwide[90]. Similar to measles, rubella is also transmitted via the respiratory route and infection results in fever and an erythematous rash[90]. As measles cases began to decline, measles surveillance systems revealed that the incidence of rubella and congenital rubella syndrome (CRS) was significant in many populations and that testing for both diseases was necessary for accurate surveillance[91]. In 2003, WHO established the Measles and Rubella Laboratory Network to strengthen capabilities for rubella and CRS case identification and confirmation[91]. The incorporation of rubella/CRS into measles surveillance systems and expanded use of rubella-containing measles vaccines in a number of countries[92] provided an opportunity for the Measles Initiative to broaden its mission and include regional rubella elimination goals as part of its measles control and elimination efforts. Now called the Measles/Rubella Initiative (MRI), the MRI strategy incorporates goals for achieving and maintaining elimination of both measles and rubella[25].

Of the six WHO regions, five have now committed to regional measles elimination goals by 2020[93]. In 2010 the World Health Assembly endorsed interim goals proposed by the WHO that by 2015 all member states should achieve 90% coverage with at least one dose of measles vaccine at the national level (80% coverage in all districts), and to achieve a 95% reduction in mortality rates from 2000 levels[93]. The

Decade of Vaccines Global Vaccine Action Plan also endorses global goals that measles and rubella regional elimination goals will be achieved in at least five WHO regions by 2020[41]. Moreover, the MRI released an eight- year (2012-2020) Global Measles and Rubella Strategic Plan that focuses support on 67 priority countries based on the level of their routine vaccination coverage for measles and status of introduction of rubella vaccine[25]. The GAVI Alliance has enhanced the impact of this support by creating a funding window for eligible countries to introduce rubella-containing measles vaccines into their national programs.

Though worldwide measles vaccine coverage has increased from 16% in 1980 to 84% in 2011, regions in Africa and SE Asia continue to report <79% coverage[5,94]. Countries with a high burden of disease that are in most need of accelerated measles control efforts are deemed priority countries. In 2008, these countries accounted for 98% of the measles-related deaths[95].

Since 2007, donor investments in the MRI have decreased by 55% and a US$10 million funding gap has led to the postponement of vaccine campaigns and campaign activities[96]. Decreasing support for global immunization programs could jeopardize the momentum gained from the accomplishments of the measles efforts. Furthermore, priority countries have not been able to raise the funds needed to support supplementary immunization activities (SIAs)[97]. As a consequence, in 2009 Africa reported a drastic resurgence of >200,000 measles cases and >1,400 deaths in 28 sub-Saharan countries[96].

Goals to reduce the global burden of measles cases are further complicated by public skepticism regarding the safety of measles vaccine, resulting in persistent suboptimal vaccination coverage in many European countries. During 2011, more than

Supplemental Immunization Activities (SIAs)

In countries with high disease incidence and low vaccination rates, supplementary immunization activities (SIAs) may be necessary. SIAs include implementing mass vaccination campaigns that effectively target a wide age range of children, irrelevant of vaccination status in order to rapidly achieve immunity in a population[433].

SIAs have been successful in reducing vaccine-preventable diseases in a number of countries and WHO regions and have been useful in strengthening the capacity of immunization programs[89,434–436].

In 1994, the Pan-American Health Organization adopted a strategy towards measles elimination that included a 3 phase approach: a “catch-up phase”, a “keep-up phase”, and a “follow-up phase”[437]. The “catch-up phase” involved vaccinating all children 9 months to 14 years old regardless of vaccination status in order to rapidly achieve high immune coverage in the population. This was then followed by a “keep-up phase” to reach susceptible infants through routine immunization services with the goal of achieving >90% vaccine coverage for each new birth cohort. Strategically implemented “follow-up” campaigns were used to vaccinate all 1- 4 year old children regardless of vaccination status to close any gaps in immunization[437]. By 1996, measles incidence in the Americas had been reduced by 99% compared to 1990 levels[24] and the WHO adopted the strategy implemented by the PAHO leadership into its recommendations[438]. In 2003, the Americas succeeded in eliminating endemic measles transmission throughout the region[24].

30,000 measles cases and seven deaths were reported from 29 countries in Europe[98]. Almost all of the cases occurred in unvaccinated individuals or in those whose vaccination status was unknown, despite the region's full adoption of the WHO recommendations[99§].

However, decrease in public demand is not restricted to developed countries and attitudes about vaccination have created challenges worldwide[100–102]. Concerted global efforts will need to enhance communication strategies regarding misconceptions about vaccines, concerns over vaccine safety, a lack of understanding of the seriousness of vaccine preventable diseases, skepticism regarding the benefits of vaccination, and religious/philosophical objections to vaccination[100,101,103]. These efforts will not only ensure continued success with measles/rubella elimination efforts, but increase demand for greater global immunizations as a whole.

Sustaining Efforts for Polio Eradication and Measles Mortality Reduction

NVAC Recommendation:

1.2 The ASH should strongly encourage the HHS Secretary to seek additional funding to facilitate the achievement of unique, time-limited opportunities to complete global goals for polio eradication and to support measles mortality reduction and regional goals for measles/rubella elimination. The ASH should advocate to the HHS Secretary that completion of these goals will yield significant economic and public health returns on investments and shedding new light on the value of vaccines and immunization and the potential for future cost-savings.

The continued march towards success for both the GPEI and the MRI are made possible through the contributions and tireless efforts of their partners in the public and private sectors. Partnerships provide opportunities to combine resources and create new synergies between programs and organizations. The CDC helped spearhead both initiatives and remains a global leader working with multilateral organizations, Ministries of Health, and others such as Rotary International, the International Federation of Red Cross and Red Crescent Societies, the Bill & Melinda Gates Foundation, and the United Nations Foundation (UNF). These partnerships are critical to achieve both the objectives of polio eradication and

§ WHO recommends that all children receive two doses of measles containing vaccine, either through scheduled routine vaccinations, or through periodic mass vaccination campaigns, depending on which strategy achieves higher coverage. A more detailed description of the WHO recommendation can be found at http://www.who.int/immunization/policy/immunization_tables/en/. (Accessed 29 December 2012).

measles mortality reduction, as well as broader international objectives for reducing morbidity and mortality due to vaccine-preventable diseases.

The NVAC specifically highlighted polio eradication and measles mortality reduction efforts because they represent time-limited opportunities that require focused political and public support if the goals are to be accomplished by the 2015-2020 target dates. Moreover, HHS continues to play a pivotal role in driving these efforts towards completion through the epidemiological, laboratory, and programmatic support that CDC provides to its partners and fellow USG agencies.

HHS Funding for Polio Eradication and Measles Mortality Reduction Activities

CDC includes global immunization activities as a line item in its annual appropriations request to Congress. The majority of this funding is allocated towards activities that support polio eradication and the control of measles and other vaccine preventable diseases within the global context. As a measure of efficiency, the program targets 90% of the annual global immunizations budget to directly support mission critical activities in the field through cooperative agreements with WHO, UNICEF, PAHO, UNF, and other USG agencies such as USAID and the State Department.

Table 3. CDC Global Polio, Global Measles and Other Vaccine Preventable Disease Appropriations (2009-2012)

Year	Polio	Global Measles and Other Vaccine Preventable Diseases
2009	$101.5 million	$41.8 million
2010	$101.8 million	$51.9 million
2011	$101.6 million	$49.3 million
2012	$111.3 million	$49.0 million
TOTAL	**$416.2 million**	**$192.0 million**

Working through UNICEF, the CDC contributed to the procurement of ~289 million doses of OPV in 2009. However, in 2010 CDC funding for polio vaccines was not sufficient to meet all country needs and the purchase of additional doses of OPV resulted in the reduction of available funds for other non-vaccine related support (e.g., operational costs) of supplemental immunization activities. Cooperative agreements with UNICEF are also in place for the procurement of MR vaccines.

Both polio eradication and global measles elimination efforts will fail if funding needs are not addressed. The spread of wild polio virus into previously polio-free countries is speculated to be related to acute funding gaps that occurred in 2002, leading to canceled campaigns and scaled back activities in Western and Central Africa[59]. The current 2012-2013 shortfall in GPEI funding has already led to reduced or canceled polio campaign activities in 24 high-risk countries in 2012. Similarly, African countries saw an explosive increase in measles cases in 2009 when countries were unable to fund supplementary immunization activities[97].

Though the funding gap cited for both the GPEI and the MRI are not solely a U.S. responsibility, increased funding for U.S. efforts does directly affect the quality and reach of these initiatives. In 2010, due to the necessary purchase of additional OPV, CDC was required to reduce operational support of supplemental polio vaccination campaign activities. While CDC maintained support to vaccinate 29.5 million children, this was well below its target to vaccinate 45 million children.

CDC Technical Assistance for Reaching Polio Eradication and Measles Mortality Reduction Goals

NVAC Recommendations:

1.3 The ASH should encourage the Centers for Disease Control and Prevention (CDC) to continue to enhance the public health impact of its Stop Transmission of Polio (STOP) Program (see below) by increasing the number and length of training opportunities. STOP Team assignments should focus on building broad subject matter expertise that can be applied to polio and measles efforts, as well as to strengthen routine immunization systems and disease surveillance.

1.4 The ASH should work with the CDC to create opportunities to bring together stakeholders and leadership from the Global Polio Eradication Initiative (GPEI) and the Measles Rubella Initiative (MRI) to discuss 1) lessons learned and best practices and 2) consider opportunities for joint programming that lead to program efficiencies and improve the delivery of vaccines using routine systems. As a leading partner in both these initiatives, CDC should work to capture and review these findings so as to inform current programming, the introduction of new vaccines, and other global public health efforts.

In addition to financial support, CDC also provides staffing support and human resources to the WHO, UNICEF, USAID, and other HHS partners. CDC technical experts conduct evaluations and risk assessments for improved GPEI and MRI activities within countries. CDC field staff conduct research studies in epidemiology, vaccine efficacy, and disease prevention and control feasibility that have contributed to operational changes to improve the impact and reach of immunization programs.

The CDC also serves as a WHO global specialized reference laboratory for polio (and other picornaviruses) and for measles and rubella. Both provide renowned expertise in virologic surveillance, virus characterization, quality assurance/quality control, and serological and specimen testing. They provide technical support and guidance for all global laboratory networks for rapid outbreak identification and response. In 2009, the CDC's Polio and Picornavirus laboratory supported the introduction of new laboratory procedures that reduced the time to detect and confirm polio infections by 50%. The CDC Measles/Rubella Laboratory facilitates measles and rubella outbreak control efforts at the national, regional, and global level to investigate and contain the spread of measles and rubella infections both within the US and abroad. These laboratory capabilities are significant, as many countries continue to lack access to certification quality surveillance for polio eradication or measles/rubella elimination.

In addition to surveillance and data collection, CDC trained staff assist countries in planning, monitoring, and managing polio eradication and measles mortality reduction efforts within the scope of their national immunization plans. This has included targeted operational support for disease control and eradication in high-risk countries. For example, the CDC is currently contributing to efforts to support Nigeria's Polio Eradication Emergency Response Plan by improving program leadership and management. However, increasing travel costs and administrative costs have reduced the overall number of technical assistance days CDC staff are able to provide. Currently, 31 CDC immunization field staff members are detailed overseas. This number is not sufficient to meet the programmatic demands of the polio eradication efforts. Additional field staff details are required.

The Stop Transmission of Polio (STOP) Program

To help meet the increasing demands for in-country support, CDC has trained and deployed over 1,550 public health volunteers on over 2,200 assignments in 69 countries as part of its Stop Transmission of Polio (STOP) programs[104]. CDC's STOP program, established in 1999, includes CDC staff and members of the international community that assist with field operations, surveillance activities, communications, and data management during three month assignments. In partnership with WHO and UNICEF, the STOP team members have provided the equivalent of 262 person-years of support to countries at the national and subnational level. Moreover, CDC has lengthened STOP team member assignments from three months to five months to meet the increasing demands for trained technical assistance by the GPEI[105] . To enhance the impact of these efforts, specialized National STOP (N-STOP) programs have been implemented in polio-endemic countries such as Nigeria and Pakistan to build country-level capacity and country-ownership to support programmatic activities. These teams facilitate the work of the GPEI, especially in areas deemed hard-to-reach due to security concerns[104].

The success of this program has created opportunities to expand the work of the STOP teams to include support for measles mortality reduction efforts, as well as other global immunization efforts including strengthening routine immunization systems and supporting more integrated disease surveillance. In 2013, it was reported that volunteers spent an average of 49% of their time on capacity building activities,

Violence and the Toll on Polio Efforts

During December 2012 and January 2013, the WHO and UNICEF were forced to temporarily suspend planned polio campaigns following a series of attacks targeting polio vaccine workers that resulted in 17 deaths.[200] The three-day campaign, which aimed to vaccinate 30 million children, involved 250,000 vaccinators[200] who are mainly Pakistani female nationals considered to be the backbone of the polio campaign.[439] Then, on February 8, 2013, attacks on clinics in Northern Nigeria resulted in the deaths of 9 polio vaccine workers just after the end of a 4-day polio vaccination campaign.[439]

Violence from militant groups on vaccination workers has been fueled by a number of factors including misperceptions about the motives behind immunization campaigns.[440,441,200] These misperceptions were aggravated in Pakistan and around the world following the CIA's use of a vaccination drive to collect information as a part of the search for Osama Bin Laden in 2011.[442] Polio vaccination in Nigeria was suspended for almost a year in 2003 due to misperceptions and unfounded suspicions of the polio vaccine and polio immunization campaigns, including beliefs that campaigns aimed to cause sterilization or AIDS.[439] Ten years later, some of these misperceptions were again stated and supported by three radio journalists only days before the February 2013 attacks, which some say ignited the violence against the polio workers.[443]

Global health organizations and the Pakistani and Nigerian governments condemned the attacks as a tragic set back at a critical moment in the fight to eradicate polio. [444, 441] However, leaders stressed the importance of continuing polio eradication work while taking precautions to protect workers and prevent opportunities for violence. Elias Durry, the head of the WHO's polio eradication team in Pakistan, stated that surgical, discrete campaigns would continue to be carried out in areas that experience polio outbreaks and heavy polio circulation.[445] Elias Durry insisted that Pakistan was ready to keep moving forward, stating that, "the bottom line is that the country is determined to finish the job."[446] Nigerian President Goodluck Jonathan stated that the Nigerian Government "will ensure that the mission to totally eradicate polio from Nigeria…is carried out to a very successful conclusion."[441]

including training of health care workers, routine childhood immunization strengthening activities, and supporting other health initiatives[104]. As polio eradication goals are completed, these programs and expertise will have continued value for other high priority immunization goals.

2. Strengthening Global Immunization Systems

Accelerated disease control efforts and mass vaccination campaigns remain important for putting countries back on track to achieve global immunization objectives. Nevertheless, each country's national routine immunization program remains the backbone of global immunizations efforts. For instance, two-thirds of the total measles deaths averted are a result of measles immunizations administered through routine programs[6,7]. Weak routine immunization systems can create barriers to reaching all children-one in every five children continues to go unvaccinated against measles[70]. Furthermore, many countries currently do not have the capability to monitor the impact of traditional EPI vaccines or introduce new and underutilized vaccines because of significant gaps in epidemiological surveillance and data collection.

The NVAC notes that strengthening global immunization and vaccine delivery systems are fundamental to increasing immunization access and coverage for children. Strategies such as better data collection and enhanced surveillance activities will improve the quality of existing programs and will translate to more children receiving the full benefits of immunization. They will also fortify the framework for incorporating future vaccines such as those for HIV, malaria, dengue, and others. Importantly, strong routine systems can serve as a platform for delivering other health interventions (e.g., insecticide-treated bed nets, vitamin A supplementation, and maternal health interventions) and building a country's immunization capacity has the potential to yield benefits across global health.

Immunization Coverage Monitoring and Disease Surveillance

Global health experts have argued, "*…the most important single contribution that public health makes to strengthening health systems is provision of relevant and scientifically valid epidemiologic data upon which to base decisions and policies affecting all aspects of the larger health system*"[27]. The outcome measure for a successful vaccination program is the reduction in overall disease burden related to the number of people vaccinated against that disease. The performance of a national immunization program is evaluated both by monitoring the accuracy and reach of vaccine coverage, and by measuring the impact the program has had on reducing the disease burden within a population. Outbreaks of VPDs can

point to program weakness such as regions where vaccination coverage is suboptimal or where a change in the epidemiology of a disease is occurring. Surveillance can also help determine whether the major contributor to disease is failure to vaccinate or vaccine failure. If the former; improving vaccine uptake would be the focus of interventions. If the latter; changes in immunization schedule (e.g., adding doses or changing ages for vaccine administration) or assuring vaccines are stored at recommended temperatures, can be implemented as possible interventions. In addition, VPD surveillance can alert the global community to outbreaks of global public health importance.

Strengthening Vaccine Data Monitoring - Estimating Vaccination Coverage

NVAC Recommendation:

2.1 The ASH should advocate for HHS efforts that support USAID, GAVI, and multilateral organizations such as WHO and UNICEF in the development of "best practices" and technologies to support countries in their efforts to more accurately track immunization coverage at the national and subnational levels and improve data quality.

Each year, national rates of immunization coverage of routine childhood vaccinations, cases of vaccine-preventable diseases (VPDs), and indicators of immunization system performance are reported to the WHO and UNICEF through the WHO/UNICEF Joint Reporting Process[106–108]. Immunization coverage estimates are based on data measuring coverage of the third dose of diphtheria-tetanus-pertussis (DTP3) among children up to 12 months of age[5,106]. DTP3 coverage serves as a surrogate indicator for access to immunization services and program performance as it requires repeated contact with a health worker over a period of time[109].

Immunization coverage data is generally used to monitor immunization program performance and data quality is important in evaluating program weaknesses and areas for improvement. Official coverage estimates are often based on administrative data of doses administered in clinics divided by estimates of the target population to be vaccinated. Doses administered data are collected by national governments via local public health authorities in the course of routine and campaign immunization program work[106,110]. Other ways to estimate coverage that may be more accurate are household survey data in which parents are queried as to a child's immunization status and usually asked to present immunization cards to verify immunization histories. These data are reported to the WHO[110], UNICEF[111], and others.

However, methodologies for collecting both administrative and survey data are often problematic[106] and recent analyses have unveiled persistent discrepancies between coverage estimates based on officially reported administrative data versus data collected through household surveys by international organizations. These differences cast doubt over the accuracy of reported DPT3 coverage levels[112–115]. In addition, coverage estimates often mask wide disparities in coverage between and within countries[116]. Better systems for monitoring and evaluating immunization coverage data are needed to manage immunization program performance and allocate resources to identify ongoing inefficiencies that impede access to immunizations and prevent programs from achieving the greatest health impact[42,117].

Administrative Data

Administrative immunization coverage data that is collected and analyzed by national public health authorities and governments is used as the basis of officially reported immunization coverage levels sent to the WHO and UNICEF by the 194 WHO member states[5,106]. This data is reported to national public health authorities and governments by health service providers such as health center staff, vaccination teams, and private physicians[106]. Estimates of immunization coverage taken from administrative data are calculated by dividing the number of vaccine doses administered to children in the target age group by the estimated number of children in the target age group within the population[5].

Administrative data may be subject to inaccuracies due to a number of factors such as staffing restraints, challenges with immunization record keeping, quality of supervision of data collection, and logistical barriers to communicating coverage data from local health clinics to higher levels of administration (e.g., Ministries of Health). Administrative data also contains possible biases in both the numerator (inaccurate and/or incomplete records of doses administered) and denominator (issues with estimates of population levels, inaccurate census data, inaccurate correction for population growth, and/or population migration)[106,112,113,118,119]. The key barriers to achieving accurate immunization coverage data are 1) poor recording and reporting of immunization data, which has the potential to deteriorate further as new vaccines are added to the immunization schedule, 2) a lack of an accurate population size estimate, which is complicated as immunization services extend past infancy and childhood, and 3) discrepancies in data from different surveys which casts doubt over reported numbers. Another criticism of administrative data is the potential for donor funding to influence officially reported immunization coverage (e.g., there may be incentives to report high coverage to show donors progress is being made)[114,120–123].

Experts and scholars have suggested that improvements to data collection systems to increase the accuracy of administrative data could include creating free-of-charge birth registers to improve the estimation of the size of the target population or establishing vaccine registries housed in health facilities[118,124]. Ideally, these information systems would be standardized and interoperable, allowing for easy data sharing. Data collection at the district level could also be improved through the increased use and improvement of district-level monitoring tools such as the WHO's District Vaccine Data Management Tool [117]. However, establishing immunization registries at the national or district level does not necessarily require the creation or uptake of new and expensive technologies to strengthen data gathering efforts. For example, the country of Oman successfully sustained immunization coverage of 98% for 10 years using a paper-based registry[118,125].

It is also shown that data quality can be improved by training health workers with basic skills to track and monitor immunization coverage, and help them to understand how data collection can inform and improve their work[122,126,127].

Governments and non-government organizations have launched a series of programs to improve vaccine coverage data and data usage, and several tools are available to improve administrative data

January 2013 GAVI Data Summit: Summary of outcomes

In January 2013, the GAVI Alliance hosted a Data Summit to discuss how to improve the quality of vaccine coverage data to achieve better outcomes and cost savings both for countries and for the GAVI Alliance. During the Summit, participants identified three priority strategic areas with corresponding actions and called on GAVI partners and others in the international community to urgently act in order to strengthen and institutionalize mechanisms to ensure data quality for learning and accountability.

Strategic area 1: Strengthen country systems and capacities

Actions:

- Develop and harmonize common frameworks for investing at the country level to improve data quality, disease surveillance and analytical capacity
- Implement a routine, systematic approach to monitoring routine data quality within all countries
- Improve denominator estimates through improved vital registration as one critical piece to better population data and therefore also more accurate coverage estimates
- Reward accurate reporting on the number and proportion of children immunized

Strategic area 2: Improve survey design, frequency, methods and content

Actions:

- Increase the frequency of household surveys. Countries with less stability or more rapid change are likely to need surveys more frequently
- Invest in improving quality and retention of home-based records
- Increase survey availability and utility at subnational levels, and further explore innovative analytical techniques that improve estimates at subnational levels
- Track full immunization status by each individual child so that full immunization can be assessed

Strategic area 3: Advance innovation in use of biomarkers, technology and triangulation

Actions:

- Consider use of available biomarkers to assess coverage data discrepancies and impact, while accelerating investment of future biomarker technologies
- Develop a systematized approach to address discrepancies between coverage estimates from different sources
- Explore the potential of mobile and digital technologies to be transformative in data quality
- Develop global and country level guidance on synthesis of data sources to improve coverage estimates and strengthen country capacities to conduct such analyses

collection and quality. The WHO's Health Metrics Network toolbox, Data Quality Self-Assessment, Revised Immunisation Data Quality Assessment, and denominator guidance tool, are available for countries to assess and improve their immunization data quality [114,128–131]. USAID's Data Quality Audit Tool and Routine Data Quality Assessment Tool verify the quality of reported administrative data[132]. Other organizations such as the Clinton Health Access Initiative, the Bill & Melinda Gates Foundation, and UNICEF also work to support countries to improve routine coverage data.

Household Survey Data

Alternative data collection mechanisms such as household survey data collection conducted and supported by WHO, UNICEF, and USAID are often considered to be more accurate and reliable than administrative data collection[118]. This includes the use of surveys such as the WHO Expanded Programme on Immunization Cluster Surveys, the UNICEF Multiple Indicator Cluster Survey, and the Demographic and Health Surveys supported by USAID. These household surveys collect immunization coverage data at the household level by gathering information on children's immunization status through immunization cards kept and updated by each family or parent. This information is sometimes supplemented by parent recall[133] (or replaced by parent recall if no immunization card is available)[118].

The WHO Expanded Programme on Immunization (EPI) Cluster Survey uses a strategy of random sampling of neighborhoods and villages, followed by sampling of a cluster of houses whose selection is based on survey worker judgment, to collect information on immunization coverage[134]. The UNICEF Multiple Indicator Cluster Survey (MICS) is a more extensive survey with a variety of health indicators[134], and relies more heavily on random sampling in order to ensure representative sampling of the population[106]. Similarly, USAID's Demographic and Health Surveys (DHS) program supports the collection of information on a variety of health and development topics[135], and relies on the selection of a representative sample of households taken from census records[136].

Despite household survey data being held as the gold standard when estimating immunization coverage[137], household survey data is also subject to a variety of biases and misreporting issues. At the household level, research has shown that the methodology used to collect information from families can be problematic[118]. Inaccuracies in survey data may arise due to the lack of availability of a vaccination card or an inaccurate record on a child's vaccination card[138]. Parents may not always receive vaccination cards, and the cards may be incomplete or inaccurate if parents neglect to bring vaccination

cards to all visits to clinics where immunizations are provided, or if healthcare providers fail to take note of vaccinations given on the vaccination card[118]. When immunization cards are not available, immunization histories must rely on parent recall. However, parent recall can also be inaccurate due to a parent's inability to recall vaccine types and doses[133,138,139], their desire to provide socially desirable responses, a lack of knowledge regarding whether another family member took a child to a vaccination appointment, or if they received incorrect information on their child's vaccination schedule from their provider[118].

Nevertheless, household survey data collection is considered essential to assure a more accurate estimation of immunization coverage and should be expanded and conducted more frequently[115,137]. Suggestions to improve and increase household survey data collection include integrating coverage surveys into other monitoring processes at the district level and into the strategic design of immunization campaigns[119,124]. Other opportunities include increasing the frequency of regular multi-topic health surveys to improve the ability to monitor both immunization coverage and other health indicators such as child mortality[114]. The applicability of these suggestions may vary depending on the scope and purpose of the household survey in question.

Household survey data quality might be improved by increasing publicity, promotion, and availability of immunization cards, and improving communication between parents and healthcare providers about what immunizations are being given and how many doses are needed[118]. It has also been suggested that data collectors should request that parents recall their children's immunizations before being asked to produce the child's immunization card, thereby allowing for more accurate analysis of parent self-report among children with immunization cards[114]. Comparison of parental recall and immunization cards with medical records and/or immunization registries might also help to improve data, if that information is available[118,133]. Experts note that it should be ensured that survey data collectors are trained and supervised adequately, and that the quality of the data is monitored regularly and corrective action taken when necessary[118].

Household survey data accuracy might also be improved through the measurement of antibody titres such as tetanus toxoid[114]. The cost of this approach could be minimized by using dried blood spots, saliva, or a random sub-sample in conjunction with immunization cards and parental recall[114]. The

comparison of the antibody titers with immunization cards and parental recall would also provide valuable information[114].

Finally, coverage levels from household surveys should be routinely compared to administrative data in collaboration with local staff and community members in an effort to progressively improve immunization data quality[118].

The HHS Efforts in Estimating Global Immunization Coverage

The CDC's Strengthening Quality and Use of Immunization Data (SQUID) Team of the Global Immunization Division (GID) works with WHO regional and country partners to improve data quality and enhance the ability of countries to conduct data analysis, interpret data, and use data for program management. At a country's request, CDC/SQUID staff will assist national immunization programs in evaluating the quality of their data and data collection systems to enhance country capacity to collect and use immunization and VPD surveillance data. CDC/SQUID conducts detailed gap analyses to help countries identify program strengths, weaknesses, areas of opportunity, and potential program threats/risks. They then work with government and public health officials to formulate action plans to address those gaps[140]. CDC also works with USAID to train immunization program managers to better perform data assessments and to implement standard procedures of data collection and verification to improve data quality.

Strengthening Global VPD Surveillance Capacity

NVAC Recommendation:

2.2 The ASH should work with other HHS offices to develop sustainable support for quality global vaccine preventable disease (VPD) surveillance systems, including the existing global and regional VPD laboratory surveillance networks. This support ideally should include technical and financial resources needed to support early warning/outbreak surveillance; laboratory diagnostics; emergency communication systems to detect and respond to outbreaks of vaccine-preventable diseases (VPDs); surveillance requirements for the eradication of targeted VPDs, including case-based polio, measles and rubella surveillance; and laboratory networks to support the introduction and monitor the impact of new and underutilized vaccines.

The important role VPD surveillance plays in strengthening capacity for global immunization systems is highlighted in the GIVS, the Global Vaccine Action Plan, the HHS National Vaccine Plan, and the CDC Global Immunization Strategic Framework[38,41,48,50]. Disease surveillance is needed to establish and monitor the burden and epidemiology of VPDs within countries in order to mobilize resources, to evaluate the performance (and impact) of each country's immunization program including the impact of newly introduced vaccines, direct response activities, inform decisions regarding the introduction of new and underutilized vaccines, and detect outbreaks of diseases with epidemic/pandemic potential. Robust VPD surveillance and access to high-quality laboratory networks are also fundamental to tracking progress towards eradication and elimination goals. For example, global polio eradication goals and regional goals for measles/rubella elimination require "certification-standard" surveillance to verify when endemic transmission has been successfully interrupted[141]. Disease surveillance data provide feedback to guide programmatic activities and improve the quality of immunization program service delivery.

Historically, VPD surveillance has been tied to disease-specific initiatives and disease-specific donor-funding. On the one hand, initiatives such as the GPEI and the MRI have created access to surveillance systems and laboratory networks in the most resource-limited countries. On the other hand, disease-specific initiatives have also led to fragmented, duplicative efforts that result in missed opportunities to coordinate information sharing and maximize limited resources (e.g., trained personnel, transport, technologies, operational/administrative space)[142–144]. Targeted disease initiatives may not represent the greatest public health concern in a country, causing conflicting priorities and unmet pressing public health needs[143,144]. Moreover, national and subnational surveillance networks supported by donor-driven priorities may not be sustainable once disease specific goals are met and funding dissipates. Finally, global goals to accelerate access to new and underutilized vaccines in low- and middle-income countries will require additional resources to create and expand surveillance and laboratory capabilities[145].

The Global Framework for Immunization Monitoring and Surveillance

To meet these challenges, WHO, CDC, and other collaborating partners developed the Global Framework for Immunization Monitoring and Surveillance ('the Framework') as guidance for strengthening surveillance and laboratory capacity for all VPDs through an approach to streamline, when possible, common processes such as data collection and management, training, reporting, and

evaluation[146]. The Framework seeks to expand access to high-quality national laboratories and WHO-accredited regional reference laboratories that can accurately diagnose viral and bacterial VPDs and to formalize VPD laboratory networks for establishing the baselines of disease burden and measuring the potential impact for newly introduced vaccines.

Resources required for adequate surveillance and program monitoring are minimal compared to program costs of implementing immunization programs. These small investments make the public health system more effective and efficient, resulting in cost savings. For example, the timely detection of outbreaks allows early control measures, reducing costs and preventing a larger number of cases and deaths. Monitoring can identify problem areas and reduce vaccine wastage[147].

The Framework also promotes linking different VPD surveillance and monitoring efforts, as well as VPD surveillance with other priority disease efforts (e.g., malaria and HIV), in order to achieve greater program efficiencies and create sustainable, country-owned programs. As the world moves closer to achieving polio eradication and regional measles/rubella elimination goals, there is a growing opportunity to use the successful platform of the Polio and Measles/Rubella surveillance systems to expand surveillance to include other priority infectious diseases (both VPD and non-VPD)[146,148].

The poliomyelitis surveillance network currently provides a structure for rapidly detecting and responding to disease of national and international importance, particularly in resource-poor countries[147]. However, recent experience trying to build surveillance for diseases preventable by the newer vaccines on the polio network suggests that polio infrastructure does not work well for all VPD surveillance, particularly for bacterial VPDs which require immediate processing of specimens. Some elements of the surveillance system can be integrated though, such as logistics for specimen transfer, supplies shipping, and overall effective laboratory management and quality control.

WHO Global Polio Laboratory Network

The WHO global polio laboratory network was established as a key strategy in achieving polio eradication through case-based surveillance of Acute Flaccid Paralysis (AFP)[141,149]. Eradication certification criteria requires that every case of AFP is investigated and confirmed through laboratory diagnostics[141]. Standardized case definitions and established guidelines for specimen collection, transport, and processing ensure the quality and sensitivity of the surveillance system[148].

The network is comprised of 146 laboratories organized in a three-tiered system that operates in all six WHO regions with laboratory-confirmed surveillance at the national, regional, and global levels[150]. Laboratories at all levels are accredited through a WHO-sponsored process that is dependent on meeting set performance standards for timeliness, workload, operational procedures, and proficiencies in isolating and serotyping virus from specimens[151].

Certification-Quality Surveillance for Polio Eradication

Eradication certification criteria states that endemic transmission of the wildtype virus must not be detected through high-quality surveillance systems (both laboratory and environmentally confirmed) for three years[141].

Acute Flaccid Paralysis (AFP) occurs in one out of every 200 cases of polio[148]. Therefore, in order to obtain certification-quality surveillance data, every case of AFP is investigated and confirmed through laboratory diagnostics. At a minimum, laboratories within the network must be able to detect at least one case of non-polio AFP per a population of 100,000 aged <15 years[149]. In addition, more than 80% of AFP cases should have two stool samples collected more than 24 hours apart and within 14 days on onset of paralysis and examined by an accredited network laboratory[447].

WHO Global Measles and Rubella Laboratory Networks

As measles control efforts increased, measles incidence subsequently declined and the global measles and rubella initiative began implementing cased-based surveillance. A key component of case-based surveillance is laboratory confirmation of suspected cases of measles and rubella. Laboratory confirmation is essential because the positive predictive value of case classification based solely on clinical presentation is very low in low-incidence settings[152].

Case-based surveillance for measles with the associated laboratory confirmation further highlighted a high incidence of rubella among populations, leading to incorporation of rubella testing into the standard testing strategy of the laboratory network[92]. This strengthened laboratory capabilities to more accurately track progress towards regional measles and rubella control goals (measles/rubella elimination or measles mortality reduction depending on the region)[23,91,92,153].

In many instances, the measles/rubella laboratory network was expanded by leveraging the existing laboratory and administrative infrastructure initially used by the WHO global polio laboratory

networks[148,152]. The WHO global measles and rubella laboratory network now includes 690 laboratories with a large number of laboratories at the subnational, national, regional and global levels[153]. The network laboratories employ a systematic testing approach using well validated assays, common quality control indicators and standardized reagents and procedures for laboratory testing and reporting[14]. The WHO provides evaluation and accreditation of laboratories to monitor performance and identify areas for further systems strengthening[153].

Integrating Disease Surveillance Systems

Both the global polio and global measles and rubella laboratory networks have successfully established high-quality national laboratories in resource-limited countries, war-torn countries, and countries with little to no public health infrastructure[148,151]. These in turn are now being utilized by countries to build surveillance capacity for other priority infectious diseases including Japanese encephalitis, yellow fever, neonatal tetanus, dengue, and rotavirus[148,153,154]. Surveillance medical officers trained in these networks have responded to outbreaks of cholera, dengue, hemorrhagic fevers, malaria, SARS, and reports of avian influenza[18,20,21].

The WHO-African region countries have used the infrastructure created from polio surveillance systems as a platform to implement an Integrated Diseases Surveillance and Response (IDSR) strategy[157]. Adopted in 1998 by the WHO AFRO-region, the IDSR strategy integrates district level surveillance activities for a number of VPDs and other high priority diseases in order to streamline resources and strengthen public health response by linking surveillance and laboratory data[144,158]. This includes monitoring for epidemic-prone diseases, diseases targeted for eradication and elimination, and other diseases of public health importance such as pandemic influenza[144]. Developed in collaboration with the CDC, the WHO, and the WHO-AFRO member countries, the IDSR strategy utilizes an action threshold approach for each specified disease that triggers coordinated activities for each tier of the surveillance system for early detection and rapid outbreak response[159,160].

At the subnational and national levels, VPD surveillance linked to formal laboratory networks can strengthen routine immunization systems and significantly broaden a country's ability to detect and respond to emerging global public health threats such as pandemic influenza[146]. However, many countries do not include VPD surveillance and laboratory support into their national immunization budget planning. Adopting strategies that integrate surveillance activities across multiple VPDs and,

when possible, linking these efforts to laboratory network capabilities, will create opportunities for sustainable, country-owned programs[146].

Building Capacity for New and Underutilized Vaccines - Expanded Disease Surveillance Needs for Successful Introduction of New and Underutilized Vaccines

Extending surveillance and laboratory capabilities to support the introduction of new and underutilized vaccines creates additional challenges for country-level programs. Recently available new and underutilized vaccines that highlighted the need for more local data include HepB, rubella, rotavirus vaccines, influenza, conjugate Hib, conjugate pneumococcal and meningococcal vaccines, and HPV vaccines.

Decision-makers need to accurately estimate disease burden of VPDs and describe their local epidemiology, to determine the costs, appropriateness, and potential impact of vaccine interventions. Surveillance capacity may need to be created or augmented in order to establish a baseline of VPD morbidity and mortality before introducing new interventions.

Surveillance for new vaccines may have different objectives than for polio and measles, which currently require nationwide, often intensive, elimination/eradication level efforts. Certain new vaccines, such as the regional conjugate meningococcal vaccine, aim at eliminating epidemic diseases and would benefit from nationwide surveillance as well[161]. The objectives of new vaccines surveillance depends on the type of evidence countries would need to help in introducing new vaccines. If local disease burden data are needed rather than relying on global estimates, countries may choose to conduct their own population-based surveillance which can be resource intensive[162,163].

Currently most countries have established hospital-based sentinel surveillance sites that can provide a description of the distribution of disease due to various pathogens; sentinel surveillance for bacterial meningitis can identify the proportion of disease due to Hib, *Neisseria meningitides*, *Streptococcus pneumoniae,* or influenza. Similarly, surveillance for diarrhea can provide the proportion due to rotavirus[146]. In addition, such surveillance can provide data on the distribution of the strains responsible for disease within a country to determine whether they match available vaccine strains and provide baseline data to subsequently assess the impact of immunization programs on strain epidemiology[45,154,164,165]. Such data has proven particularly helpful for diseases caused by multiple strains

that are not all contained in the new vaccines, such as for meningococcal, pneumococcal, influenza, and rotavirus vaccines. For those diseases where sentinel surveillance is usually the only surveillance system available (e.g., invasive bacterial disease [IBD] and rotavirus surveillance), measurement of impact on a nationwide basis is not possible or must be estimated.

In addition, in well performing sites, case-control and other studies can be conducted to evaluate vaccine effectiveness. Immunization program managers need to be able to measure the impact the vaccine has on reducing disease burden once interventions are widely introduced. Moreover, surveillance data must be collected over a sufficient time frame to accurately capture the epidemiology of disease in a given region. WHO, in partnership with CDC and others, has recently published guidelines to help countries evaluating the impact of new vaccines such as rotavirus, Hib and pneumococcal conjugate vaccine[166,167]. New vaccine sentinel surveillance has been more readily achievable for rotavirus, for which it was easier to use some of the existing polio surveillance infrastructure, but has been much more challenging for invasive bacterial disease surveillance, where developing adequate capacity for bacteriology requires more intensive support and rapid processing of specimens such as cerebral spinal fluid.

Finally, subnational and national laboratories must be able to absorb this greater workload without unnecessarily taxing the existing VPD surveillance systems. Unlike polio and measles/rubella surveillance networks, funding for these expanded activities is not broadly supported by global initiatives and lower and middle income countries may struggle to meet the core capacities required to inform public health investments in these newer vaccines[146].

Establishing Global Surveillance and Laboratory Networks New and Underutilized Vaccines

Surveillance for VPDs can vary greatly by district and geographic region complicating the ability for decision-makers to compare data and establish baselines of VPD burden. In order to facilitate meaningful, evidence-based decision making, several initiatives have begun to formalize and systematize epidemiologic and laboratory surveillance for diseases targeted by new and underutilized vaccines. The initial framework for the Global Invasive Bacterial Disease Surveillance Network was laid by participating sites that incorporated standardized case definitions and common data reporting methods to monitor the burden of meningitis, pneumonia, and sepsis caused by *Haemophilus influenza*

Type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis* [45,164,165]. Similar efforts have led to the establishment and expansion of the WHO Global Rotavirus Surveillance Network[154].

Integrating surveillance for these diseases into existing programs and routine systems at the subnational level has also facilitated data collection for the introduction of new and underutilized vaccines. The CDC led preliminary efforts to utilize the existing polio and measles/rubella networks in Bangladesh, China, and India to monitor for viral and bacterial VPDs causing acute meningitis/encephalitis syndrome (AMES) and acute encephalitis syndrome (AES)[168]. Similarly, other countries have demonstrated the feasibility of honing surveillance for meningitis/encephalitis syndromes by integrating both viral and bacterial laboratory testing for case confirmation[169].

For underutilized vaccines such as seasonal influenza, robust surveillance systems are already established and can be expanded to further provide the evidence base supporting greater uptake of seasonal influenza vaccines in developing countries. Global influenza virological surveillance has been conducted through WHO's Global Influenza Surveillance and Response System (GISRS) for over half a century. Formerly known as the Global Influenza Surveillance Network, the new name came into effect following the adoption of the Pandemic Influenza Preparedness Framework in May 2011. WHO GISRS monitors the evolution of influenza viruses and provides recommendations in areas including laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment. WHO GISRS also serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential. National Influenza Centres (NICs) collect virus specimens in their country and perform preliminary analysis. They ship representative clinical specimens and isolated viruses to WHO Collaborating Centers for advanced antigenic and genetic analysis. The results form the basis for WHO recommendations on the composition of influenza vaccine each year, as well as relevant risk assessment activities of WHO. NICs are national institutions designated by national Ministries of Health and recognized by WHO. They form the backbone of the GISRS. There are currently 140 NICs in 117 countries.

The Role of HHS in Global VPD Surveillance

All VPD laboratory networks are tiered, with the number of levels dependent on the surveillance questions addressed at each level, the technical capabilities achievable at each level, and the resources available for the network. Most networks have at least three levels, originally designated as National

Laboratories, Regional Reference Laboratories, and Global Specialized Reference Laboratories. As the VPD laboratory networks have matured, capabilities continually develop in the more local laboratories, facilitating their ability to perform laboratory procedures initially defined for the Regional and Global Specialized Reference Laboratories. Formal accreditation procedures have been developed for each level in the VPD laboratory networks. Consequently, the network structure becomes flexible, and an important role of the Reference Laboratories is to support introduction of the most powerful and appropriate technologies into the entire network.

The CDC serves as a Global Specialized Reference Laboratory to a number of WHO-coordinated laboratory networks including the Global Polio Laboratory Network, the Global Measles/Rubella Laboratory Network, the Global Rotavirus Surveillance Network, the Global Influenza Surveillance and Response system, and the Global Invasive Bacterial Disease Surveillance Network, as well as regional surveillance and laboratory networks for yellow fever, Japanese encephalitis, pediatric bacterial meningitis, and hepatitis B. The responsibilities of Global Reference Laboratories vary with the disease agent but include distribution of reagents, cell lines, primary virus and bacterial isolation and confirmation, quality control/quality assurance of the networks through development and distribution of proficiency panels, parallel testing of specimens, serotyping or serogrouping, genetic sequencing, serological diagnosis, PCR and other technology transfer, training of Regional Reference Laboratories and selected national laboratories on advanced diagnostic techniques, troubleshooting, consultation, accreditation reviews, development of new diagnostic methods and reagents, participation in Regional and Global laboratory network meetings, and research relevant to surveillance needs.

In addition, CDC has recently participated and co-partnered with the WHO, non-governmental organizations, and academic institutions on many vaccine introduction initiatives supported by the GAVI alliance, such as the Pneumococcal conjugate Accelerated Development and Introduction Plan (Pneumo-ADIP), the Rotavirus Vaccine Program, the Hib Initiative and the Accelerated Vaccine Initiative Technical Assistance Consortium. Through these initiatives, funding was provided to support multiple surveillance activities to measure diseases burden and monitor the impact of newly introduced vaccines[45,170].

CDC's Influenza Division has supported more than 50 countries since 2003 to develop laboratory and epidemiologic capacity to conduct surveillance for influenza disease, both hospital and clinic based,

using WHO standard case definitions for Severe Acute Respiratory Illness. These systems allow for assessment of virologic characteristics of circulating influenza viruses, clinical characteristics of strains and data to assess burden and impact of intervention such as vaccination. These platforms can be used for other respiratory pathogens. Regional Networks such as the Africa Network for Influenza Surveillance and Epidemiology (ANISE) also allow for standardization of epidemiologic surveillance. In addition, the Influenza Division also directly supports more than one hundred domestic state, local, and military laboratories by providing diagnostic testing kits, ancillary reagents, and staff through the Influenza Reagent Resource (IRR) and Epidemiology and Laboratory Capacity (ELC) for Infectious Disease programs.

Although not focused primarily on VPD surveillance, the CDC's Global Disease Detection and Emergency Response program contributes to strengthening VPD surveillance and laboratory capacity at the global, regional, and local levels by improving public health preparedness and response during humanitarian emergencies and outbreaks of global health importance[171]. The program serves to build the country-level surveillance capacity needed to implement the International Health Regulations (IHR)[172]. As a liaison to the WHO Global Outbreak Alert and Response Network (GOARN), the GDDER has assisted in response efforts for a number of VPD outbreaks including measles, meningitis, polio, and cholera outbreaks[171]. Moreover, the program has supported the expansion of existing polio and measles/rubella laboratory networks for broader VPD detection and response[168].

Building Country-level Surveillance Capacity through the CDC's Field Epidemiology and Laboratory Training Programs (FELTPs)

NVAC Recommendation:

2.3 The ASH should work with CDC to increase core support to the CDC's Field Epidemiology and Laboratory Training Program (FELTP) as a key tool to transferring epidemiologic and laboratory capacities for strengthening programs. This support should specifically be used to incorporate immunization topics into FELTP training.

One important barrier to incorporating sustainable VPD surveillance and laboratory networks into routine immunization programs is an insufficient number of competent, trained public health personnel[146]. Developing a trained public health workforce is a key building block of systems strengthening[173,174] and strengthening immunization systems at the national and subnational levels

includes creating training opportunities as part of a country's public health infrastructure. The CDC-supported Field Epidemiology and Laboratory Training Programs are a proven strategy to develop locally-trained personnel in applied field epidemiology and laboratory practices for VPD surveillance and response[173,174].

The Field Epidemiology Training Program (FETP) is modeled on the CDC's Epidemic Intelligence Service and consists of a two-year, full-time program that incorporates classroom training and field assignments[175]. The Field Epidemiology and Laboratory Training Program (FELTP) includes an additional competency-based training component to support laboratory surveillance and outbreak response[175]. Eligible participants are typically junior to mid-level employees in-service to a country's Ministry of Health[174]. Training modules consist of courses in epidemiology, communications, economics, monitoring and evaluation of surveillance systems, achieving performance measures for disease control and prevention, and program management[175]. Graduates of the program are capable of operating national public health surveillance and response programs and are expected to go on to train additional personnel. Since 1980, the CDC has developed 41 Field Epidemiology Training Programs that serve 57 countries. The program has graduated over 2,300 trainees and has greatly contributed to augmenting the global public health workforce[27,176,177]. FE(L)TPs also provide short courses and training workshops for surveillance officers and front line public health workers at the subnational levels.

FE(L)TPs are initiated in countries through partnerships with the CDC, the WHO, country Ministries of Health, and donors or development agencies such as USAID and others[174]. CDC provides an in-country resident technical advisor to aid in the program development and training for four to six years, and countries are expected to take on increasing financial and technical responsibility of the program over time to ensure long-term country-driven sustainability.

The CDC also collaborates to coordinate FE(L)TP programs at the global level through the Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET). TEPHINET is a professional alliance of more than 55 FE(L)TPs around the world (http://www.tephinet.org/). With over 80 participating countries, TEPHINET joins national and regional FE(L)TP programs to support information sharing and best practices through scientific conferences, meetings, and training workshops[178]. The TEPHINET Secretariat, in collaboration with program directors, has also created criteria and processes for program accreditation and quality improvement[178]. These coordinated

networks FE(L)TPs are now playing a major role in developing a sustainable global public health workforce.

Improving the Delivery of Immunization Services - Reaching Every District/ Community

NVAC Recommendation:

2.4 The ASH should support the work of HHS within the international community to define standards for measuring the impact of routine delivery strategies such as the Reaching Every District/ Community (RED/C) strategy. These metrics can be used for the evaluation of how well these strategies perform in fully vaccinating children with routine immunizations.

Though global immunization coverage with DTP3 has risen to 83% in 2011 from only 23% in 1981[179,180], large inequalities between and within countries continue to exist. Closer examination of global immunization coverage reveals that despite overall gains, low-income countries continue to have lower immunization coverage than high-income countries, and significant disparities continue to exist between wealth quintiles where the poorest children are the least likely to receive immunizations[116,181]. For example, in India, which is home to about one-third of the world's unimmunized children, the overall national coverage rate of DTP3 in 2010 was 72%[116]. However, in Indian states such as Mizoram, coverage rates between the richest and the poorest children differed by 71 percentage points[116]. In the state of Arunachal Pradesh, only 8% of children in the poorest quintile were fully vaccinated with DTP3[116].

In addition, the average DTP3 coverage rate for low-income countries in 2010 was shown to equal the average DTP3 coverage rate for high-income countries in 1986, meaning that low-income countries are more than 20 years behind[116]. In a survey of the literature, it was found that factors such as lack of access to immunization services, poor quality of health services, missed opportunities, hidden financial and opportunity costs to families, and lack of vaccine availability were the most cited reasons for why children are not immunized[116,182].

Children in hard-to-reach rural areas are less likely to be immunized due to geographic restrictions, such as distance from health clinics, physical geographical barriers, and the difficulty of travel for health workers[116,183–190]. Children living in urban slums are less likely to be immunized due to a lack of access to health information and/or a limited interchange of information regarding immunization services[191,192]. Mobile populations and nomadic populations have lower immunization coverage as they are often

overlooked during immunization campaigns and delivering subsequent doses of vaccine becomes difficult once population groups have moved to another location[190,193,194]. Finally, during times of political unrest or violence, immunization activities are sometimes temporarily halted, leaving children unimmunized[195–199], such as following the recent violence against polio workers in Pakistan[200].

In response to the challenges of immunizing these hard-to-reach children, the WHO, UNICEF and other partners in the GAVI alliance developed the Reaching Every District/community approach (RED/C) in the Africa region[189,201]. The RED/C approach uses five tactics in an effort to overcome common obstacles to increasing immunization coverage among hard-to-reach populations, with a special focus on planning and monitoring[201]. The five elements of the RED/C strategy include:

- **Re-establishing outreach services** to all communities;
- **Supportive supervision** of health workers, including on-site training, regular visits, and assistance with problem solving;
- **Linking services with communities** to increase community participation and ownership;
- **Monitoring and use of data for action** to make adjustments and improvements in vaccine delivery; and
- **Planning and management of resources**, including microplanning for each district based on a local situation analysis.[201]

The RED/C approach also encourages the use of coverage data to prioritize districts that need the most help in improving access and utilization of immunizations, along with the use of microplanning to address local problems with solutions that are appropriate to the community[189]. Since 2002, most countries in the WHO regions of Africa, Eastern Mediterranean, Europe, South-East Asia, and the Western Pacific have utilized the RED/C in their efforts to extend routine immunization to all populations[202].

Evaluations of RED/C implementation in the Africa region and Assam, India have shown overall good results[203–205]. Although the authors indicate that it is difficult to attribute improved vaccine coverage directly to implementation of the RED strategy, the overall quality of immunization programs improved in intervention districts[203–205]. For example, implementation of the RED/C approach reportedly increased frequency of supportive supervisory visits to local immunization providers with increased constructive feedback on how to improve immunization services[203].

Researchers that conducted these evaluations noted that further research is needed to examine the sustainability of the impact of the RED/C approach on immunization coverage, and that variability in the interpretation of the RED/C guidelines leads to diverse implementation strategies across countries[204,205]. Additionally, though many countries in several WHO regions have implemented RED/C, only 11 have undergone in-depth country-level evaluations of their implementation of the program, and all have been in the African region[203,204]. Researchers also noted that several of these countries were selected for evaluation on a volunteer basis, indicating that the sample of countries being evaluated was not necessarily representative, and within each country a limited number of districts were visited[203].

HHS Evaluation of Immunization Strategies – Reaching Every Child

CDC has been an important contributor to developing and evaluating strategies to reach every child with vaccines, but more work is needed. In 2008, WHO's Scientific Advisory Group of Experts on Immunization requested more information on 'the epidemiology of the unimmunized child'. In response to this request, the WHO coordinated a three part review of current literature and available data to explore the reasons and factors linked to low vaccine uptake in low and middle income countries[206]. The Global Immunization Division (GID) at CDC conducted the review of the peer-reviewed literature.

A total of 901 reasons and factors associated with the under-vaccinated child were identified from these 209 articles. Of these reasons and factors, 393 (44%) were related to immunization systems, 255 (28%) to parental attitudes and knowledge, 199 (22%) to family characteristics, and 58 (6%) were associated with communication and information. Thirty-three reasons and factors were abstracted from 12 articles describing the completely unvaccinated child. Of these, 4 (12%) were related to immunization systems, 18 (55%) to parental beliefs and knowledge, 9 (27%) to family characteristics, and 2 (6%) to communication and information. The distribution of reasons and factors associated with these four major themes were relatively constant over the review period[206].

Several common themes were identified in this review to describe the epidemiology of the under-vaccinated child in low and middle income countries. Access due to geographic barriers (e.g., living in remote/rural areas, clinic too far away) and missed opportunities to vaccinate (e.g., not having a vaccination card at time of visit), for example, were linked to low vaccine uptake in most countries from

which articles were identified. Other reasons and factors, especially those linked to parental attitudes and knowledge, such as role of gender, regionally focused and more difficult to interpret. Many of the identified parental attitudes and regarding vaccinations may be 'proxies' for more complex health seeking behaviors and perceived barriers[206].

Strategies to Improve the Vaccine Supply Chain

Insufficient vaccine supply chains can further exacerbate challenges to providing immunization services for hard-to-reach populations. Poorly-managed or under-resourced logistics systems can weaken already fragile immunization programs, and weak systems can lead to significant vaccine wastage, adding to program costs and resource constraints[207]. Furthermore, inadequate vaccine supply chain capacity may cause unnecessary delays in the introduction of new vaccines as national immunization programs struggle to incorporate transport and storage requirements for increasing volumes of vaccine products[207].

These considerations have spurred a number of global initiatives to innovate and fortify these systems. USG efforts towards global vaccine supply chains and logistics are predominantly supported by USAID with contributions by HHS agencies mainly serving as representatives on advisory panels. However, the NVAC has highlighted a few examples of global initiatives here as they represent important contributions to the goal of achieving strong, well-functioning immunization delivery systems.

The Five Tenets of Improving Vaccine Supply Chains[207,448]

The following steps have been identified as critical to achieving strong immunization logistics and supply systems:

1. Introduce innovative vaccine products and packaging tailored to meet the needs and constraints of developing countries.

2. Facilitate efficient and effective vaccine delivery and leverage proven methods from other sectors.

3. Assess and minimize the environmental impact of energy, materials, and processes used.

4. Design information systems to help plan and manage immunization activities and resources while ensuring that adequate quantities of vaccines are always available to meet demand.

5. Include human resources policies that provide adequate numbers of trained, motivated, and empowered personnel at all levels of the system.

UNICEF Cold Chain and Logistics (CCL) Taskforce

The UNICEF-led Cold Chain and Logistics Taskforce first met in 2007 as an initiative to strengthen and expand vaccine supply chain capacity within national immunization programs[208].The Taskforce is divided into five subgroups focusing on guidance, monitoring, advocacy, integration, and systems of the future[209].

Early efforts of the task force involved a collaboration with Project Optimize (described below) and numerous other CCL partners and stakeholders to define a common vision for the future of vaccine supply chains and to create a roadmap for aligning CCL capacity-building efforts at all levels (global to program level) under five identified areas of need[210]. The vision driving these efforts states that "*by 2020, the capacity of National Immunization Programmes is strengthened so that every individual can benefit from vaccines of assured quality delivered in the right amount at the right time through efficient logistics, proper vaccine management, and a well-functioning cold chain system"*[209].

More recently, CCL Taskforce discussions have included defining performance indicators, evaluating tools for assessing vaccine supply chains within countries, and discussing ways to improve management of supply chains (e.g., minimizing wastage, better forecasting needs)[211]. The UNICEF CCL Task Force has collaborated with TechNet-21.org, to provide a webpage offering recommended guidelines and best-practices for better management of national vaccine supply chain and logistic systems[212]. TechNet-21.org is an online community resource center that has contributed discussion forums, document libraries, and numerous other tools and resources for strengthening immunization services since 2005[212].

UNICEF is now partnering with WHO and TechNet to create an Immunization Supply Chain and Logistics Hub (iSCL Hub) to serve as a global resource center for vaccine supply chain and logistics knowledge and expertise. The iSCL Hub will provide partners with resources, guidelines, policies, and technical assistance for capacity building and coordination of on-going CCL initiatives to create synergy between parallel efforts. Work to establish the iSCL Hub was initiated in January 2013 (WHO, personal communication).

Project Optimize (2007 – 2012)

Project Optimize (2007-2012), led by the WHO and PATH, with funding from the Bill & Melinda Gates Foundation, was initiated to innovate, demonstrate, and facilitate advances in the vaccine supply chain through the use of new and emerging technologies[213]. In 2008, Optimize conducted a number of landscape analyses and stakeholder workshops to provide a comprehensive picture of the existing vaccine supply chain in order to develop a strategy to focus efforts on key areas that would benefit most from technological and scientific advances[214]. Moreover, these initiatives would benefit not only immunization systems, but also supply chains for other pharmaceutical products used by global health

initiatives (e.g., maternal health interventions). Optimize considered better coordination with the private sector[215] as well as new cool chain technologies. For example, innovation projects resulted in the use of passively cooled produce carts to transport greater volumes of vaccines at more consistent temperatures than could be attained with traditional vaccine cold boxes. Advances in battery-free, solar-powered refrigerators were explored to aid communities that lack reliable access to electricity[216].

In addition to innovations in equipment, Optimize has also supported the development of information systems, technologies, and operational models that were tested and evaluated in the field. The results of these projects and other information are shared at conferences, workshops, in a quarterly newsletter (*Op.ti.mize)* [213]*,* and on the PATH, WHO and TechNet-21.org websites. To make sure that the progress made by Optimize continues as the initiative itself comes to an end, Optimize has developed a traveling exhibit entitled *Supply Systems for Today and Tomorrow* to reach audiences and share information on how different countries can use the knowledge of potential solutions and remaining gaps to improve their own vaccine supply chains and logistics systems[217].

Building off the accomplishments and areas of opportunity highlighted by Project Optimize, GAVI has also initiated larger efforts to prepare an end-to-end vaccine supply chain strategy. The GAVI end-to-end strategy under development is anticipated to be released in late 2013.

One of Project Optimize's most notable collaborations has been to demonstrate the feasibility of delivering vaccines using a controlled temperature chain versus the traditional cold chain (where vaccines are maintained at 2-8°C). Controlled temperature chain (CTC) is defined as *storing and transporting vaccines in a controlled temperature chain within a temperature range appropriate to the particular vaccine's heat stability profile*[218].

The vaccine MenAfriVac™ was developed specifically for the protection against Type A meningococcal disease in sub-Saharan Africa[219]. However, many countries that make up the "meningitis belt" have limited cold chain capacity and pose difficult challenges to vaccine delivery. Promising data from the manufacturer indicated that MenAfriVac™ was stable for a limited time at temperatures up to 40°C, making it a suitable candidate for the CTC approach.

Working with the Drug Controller General of India, Health Canada, and the manufacturer, WHO and PATH were able to obtain a license variation for MenAfriVac™, and immunization campaigns using CTC to deliver the vaccine began in November 2012 in northern Benin[220]. The system included temperature indicator cards to designate whether the vaccines exceeded the maximum temperature threshold as well as individual vaccine vial monitors to monitor each vial's cumulative exposure to heat[220]. The CTC approach was considered easy to implement and preferable by vaccinators and supervisors. Moreover, the CTC approach showed numerous benefits including reduced wastage and greater flexibility as health workers could travel several days to reach target populations without having to return each night to the health post[220,221].

Use of existing vaccines outside the traditional cold chain has the potential to reduce costs, increase program flexibility, and improve the number of people reached by vaccination efforts (particularly underserved and hard to reach populations). However, data must support that temperature variations do not affect the safety and efficacy of a vaccine[222]. Delivery of vaccines using the controlled temperature chain will require additional regulatory guidance and oversight. The FDA's Center for Biologics Evaluation Research (FDA/CBER) is working with the WHO to develop scientifically appropriate guidelines for vaccine use that can be used to support handling at the temperature extremes encountered during vaccine transport and delivery during immunization campaigns. Addressing these key issues will be necessary to further facilitate distribution of other vaccines such as hepatitis B and oral polio vaccines.

Vaccine Presentation and Packaging Advisory Group (VPPAG)

The Vaccine Presentation and Packaging Advisory Group (VPPAG) is a forum in which the public sector can engage vaccine manufacturers on issues related to vaccine packaging and presentation to better support the development of products suitable for the capacities and operational capabilities of developing countries to facilitate vaccine introduction and uptake[223]. Originally established by GAVI in 2007, the forum is now a subcommittee under the WHO's Immunization Practices Advisory Committee. The VPPAG includes members from the International Federation of Pharmaceutical Manufacturers and Associations, the Developing Country Vaccine Manufacturers Network, WHO, PATH, UNICEF, CDC, USAID, GAVI, and the Bill & Melinda Gates Foundation, and others[224]. They have provided guidance to industry on issues such as reducing vaccine packaging volumes to accommodate limited cold-chain storage capacity in developing countries, guidance on the use of vaccine preservatives in multi-dose

vials, and recommendations for identifying the desired target attributes ("target product profiles") of future vaccines in the development pipeline[223].

Recently, the VPPAG has explored the use of two-dimensional barcodes on vaccine labels and packaging in developing country vaccine supply chains[225,226]. Two-dimensional barcodes improve the tracking and tracing of vaccines, strengthen stock control and improve patient safety[225]. In support of these efforts, GAVI is working with its partners to develop standards for manufacturers, including guidance regarding the type, format, and information that should be included in vaccine packaging barcodes. Feasibility testing of this technology to track vaccine stock movements from the national to regional to district level is currently being conducted in Tanzania[226].

Integrating Preventive Health Services with Immunization Programs to Optimize Health Delivery Systems

NVAC Recommendation:

2.5 The ASH should work with the Office of Global Affairs and CDC to assist national governments, development agencies (including USAID), multilateral organizations (including WHO and UNICEF), and civil society in encouraging the use of immunization contacts (both through routine systems as well as campaign activities) as a platform for delivering additional health and aid services and vice versa. Evaluations of these efforts should include the types of interventions, the cost benefits of combining new interventions with global immunization efforts, and the effect these strategies have on building community demand for health services overall.

Vaccines address a limited but important range of specific diseases, but many vaccine programs do not comprehensively address other major public health problems (e.g., vector-borne disease prevention, HIV testing, and availability of contraception, etc.). When health services are delivered independently, incentives to use essential public health services may decrease[201], negatively affecting overall participation in health prevention programs. Conversely, evidence indicates that where health centers offer a range of services, vaccine coverage rates tend to be higher[227]. For example, a study in Zambia that linked immunization to multiple child health interventions in a routine setting (e.g., growth monitoring, vitamin A supplementation, family planning and health education) was associated with a significantly improved proportion of children who were fully immunized[228].

The current state of the global economy creates circumstances where global health programs are competing against multiple health and non-health priorities for scarce donor and in-country resources. Using patient-centered approaches to combine strategies among immunization and non-immunization programs, especially where programs are synergistic, can potentially decrease competition for resources and reduce intervention-specific costs, especially where transport and distribution mechanisms are shared[20,145,227]. In addition, efforts to link immunization with other essential health interventions can lead to improved efficiency in public health services, and broaden the partnership base. For example, the Global Action Plan for the Prevention of Pneumonia and Diarrhea (GAPPD) is a program that has set goals and strategies to scale interventions such as immunizations with strategies such as breast-feeding promotion and antibiotic treatment[229]. Similar integration models have been developed by WHO[227,230].

A recent study of NGO-facilitated projects utilizing community-based intervention packages found improved coverage for multiple high-impact interventions simultaneously at the scale of one or several districts[231]. All projects analyzed in a community based intervention were effective in rural settings in Africa, Asia, and the Caribbean with moderate to high child mortality and all were in countries prioritized on the Countdown to 2015 list[231], which tracks coverage levels for health interventions proven to reduce maternal, newborn and child mortality. Coverage levels for all interventions substantially increased in spite of weak settings[231]. In a health survey in sub-Saharan Africa, researchers found that if non-vaccine interventions were integrated with routine vaccination, coverage for all interventions examined could be substantially higher than current levels[232]. Dramatic increases in coverage of several critical interventions, as high as five to 15 times the current levels, could theoretically be achieved in sub-Saharan African families through such linked delivery[232].

The ability to efficiently deliver multiple non-vaccine interventions along with routine vaccinations would depend on many factors, including acceptability of the selected services to the public and to health providers, ability to augment facilities to provide adequate storage for commodities (such as bed nets) and privacy for delivery of sensitive services (such as HIV testing and contraception), sufficient staffing and training of health providers to ensure that the added services do not place undue burden on vaccination programs, financing and logistical support, and improved monitoring and evaluation tools[232].

Integrating other health interventions with immunization at outreach sessions requires a series of carefully planned and implemented steps. These steps include selecting interventions that can be feasibly integrated at the outreach level, instituting inter-sector coordination at all program levels, exploring service funding sources, conducting joint training and supervision of health workers and program managers, ensuring the participation of community-based organizations, leaders, and volunteers, and establishing a robust monitoring and review mechanism that provides timely information to communities, health workers, program managers and policy makers[233].

Integrated programs have the potential to deliver a multitude of services; however, they can be compromised due to lack of political and financial commitment, shortages of human resources, inadequate monitoring and information systems, and lack of management skills, among others[145]. The unique situation and priorities of each country, along with available resources and any potential impact on existing vaccination programs, must be considered when determining whether and which services to integrate with routine vaccinations.

Examining the theoretical impact of integration is the first step in quantifying and capitalizing on the true potential of integrating delivery of other health services with routine vaccinations[232]. By incorporating scientific evaluation into integration efforts, programs can mitigate the risks that are intrinsic to the bundling of services or systems. Scientific assessments of integrated programs can reveal surprising results and can highlight the key areas that need focus for the successful scale-up of integration efforts[234]. When the integration of diverse interventions is being examined, five factors should be examined: coverage, quality, acceptability, complexity, and unintended consequences. It cannot be taken for granted that coverage, quality, and acceptability of immunization will immediately translate to an effective integrated program[234].

HHS Support of Efforts to Integrate Preventive Health Services with Immunization Programs

CDC has been in the forefront of evaluating the role of immunization systems as a platform on which to build a robust public health system through the appropriate integration of other health services, and has recently sponsored, and contributed to, a special journal supplement devoted to this issue[235]. CDC works with other global immunization partners to incorporate strong evaluation and operations research into the integration of services and systems to ensure successful integration and the absence of unintended

consequences such as the erosion of acceptance, program performance, or the quality of individual services.

Ensuring Immunization Coverage among U.S.-bound Refugees

NVAC Recommendation:
2.6 The ASH should endorse HHS coordination with other USG agencies to support efforts that provide routine overseas administration and documentation of vaccinations for all U.S.-bound refugees with vaccines that have been identified for pre-departure administration.

Complex emergencies can create situations that promote the spread of vaccine-preventable diseases among vulnerable refugee populations. In many of these countries, immunization levels are typically lower than most developed countries, and routine health services may break down for extended periods of time due to instability prior to, during, and after a complex emergency[113,235–241]. Additionally, refugees often temporarily relocate to refugee camps and urban slum settings where they experience crowding, high population density, inadequate sanitation, malnutrition, and a scarcity of clean water, which create ideal conditions for the spread of vaccine-preventable diseases such as measles, mumps, cholera, meningitis, and yellow fever[113,236–238,242–248]. Measles is particularly dangerous in crowded refugee camps and urban environments, as high-population density creates ideal conditions for measles to spread, creating heightened risks for children in complex emergencies[236–238,244–246].

Targeted and rapid vaccination campaigns are critical to controlling disease outbreaks, particularly measles outbreaks, during complex emergencies[113,236,244,245,249,250]. It's been shown specifically that measles vaccination with SIAs during complex emergencies is a very cost-effective prevention strategy[244]. Proper vaccination of refugees in transit camps and surrounding areas also prevents delays in relocation to the receiving country[251].

Complex emergencies such as political conflicts and other humanitarian crises account for 50,000 to 75,000 refugees to enter and resettle in the United States each year[252,253].The U.S. has the largest refugee settlement program worldwide[252,254]. In fact, over 650,000 refugees have resettled in the U.S. since 2000[254,255]. Refugees are not required to be vaccinated or provide proof of vaccination before entering the U.S. and immunizations are thus provided after their arrival[239,252,253,256,257]. Currently, many refugees arrive from countries with low vaccination rates, possessing poor vaccination documentation,

or no documentation at all[258], resulting in concentrated populations susceptible to vaccine-preventable diseases[240,258–264].

Immunization of refugees prior to their arrival to the U.S. can prevent costly outbreak control efforts and added morbidity caused by disease importations[252,256,257,263,265]. After resettlement, refugee children are vaccinated through the Vaccines for Children Program, and coverage for vaccination of adult refugees depends on the laws and policies of the receiving state[257]. Certain adult vaccinations are covered for refugees by Refugee Medical Assistance, a program of the HHS Office of Refugee Resettlement which provides funds to states for post-arrival medical screenings for refugees[257,266*]. Although immunization does not usually occur until after resettlement in the U.S., there is a 4-6 month period between their required overseas health assessment and their arrival when immunizations could be administered[267,268]

Immunization catch-up after arrival and resettlement may be inadequate, with one study demonstrating only 51% of refugee children are completely up-to-date on immunizations one year after resettlement (much lower than the national average that year of 77%)[264]. In another study, 23% of refugees never completed their initial health assessment necessary to determine which vaccines were needed after arrival to the U.S. due to loss-to-follow-up when they moved to another state, refusal to receive the health assessment, missed appointments, or provider failure to follow protocol[260].

It has been shown that in addition to the cost-saving through the prevention of disease importations, the estimated cost of immunizing refugees overseas prior to arrival in the U.S. is substantially lower due to the lowered cost of vaccines provided internationally by UNICEF. Immunization of all U.S.-bound refugees in their country of origin is estimated to cost up to 11 times less than the cost to immunize these populations after their arrival (UNICEF prices would equal roughly US$365,000, compared to US$4.2 million [U.S. federal contract price])[267]. The administration fee for these immunizations is also lower overseas, at an estimated US$6 /dose versus US$13/dose within the United States[267].

* Immigration and Nationality Act Section 212 (8 U.S.C. 1182)(a)(1)(A)(ii) as amended by section 341 of the Illegal Immigration Reform and Immigrant Responsibility Act of 1996.

The HHS Efforts to Promote Pre-Departure Immunization of US-Bound Refugees

Currently, the CDC Division of Global Migration and Quarantine (DGMQ) and the HHS Office of Refugee Resettlement (ORR) are collaborating with the State Department and others to analyze the economic benefits of overseas vaccination. In addition, CDC/DGMQ and the State department are collaborating with partners to conduct a vaccination pilot program for U.S.-bound refugees in five countries. These efforts are intended to support a policy shift in the near future to provide selected routine vaccinations and possibly other preventive medical interventions, overseas to U.S.-bound refugees.

Vaccine Advocacy: Increasing Global Demand for Vaccines

Ensuring adequate rates of coverage cannot be achieved without a high level of community acceptance and demand for vaccines, regardless of the strength of immunization programs. The Decade of Vaccines Global Vaccine Action Plan's second strategic objective is that "individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility"[41]. When disease incidence is high, the benefits of vaccination are clear and more accepted by the public. However, as traditional and new vaccines continue to drive down the burden of disease, populations are beginning to face a change in risk perception where the risks associated with vaccination are disproportionately weighed against the benefits of preventing disease[269]. This may be further amplified by the propagation of misinformation about the safety of vaccines or adverse events falsely attributed to vaccination[269]. This has been most clearly demonstrated recently in Pakistan and Nigeria where inadequate acceptance of polio vaccines has contributed to the continued spread of polio over the past decade[270,271].

While the roots and patterns of these concerns are not completely understood, public health researchers are actively studying ways to analyze factors that contribute to community demand for vaccines. Current studies are investigating global patterns of vaccine safety concerns being voiced in news and social media to better understand and address concerns and misperceptions of vaccine safety[272,273]. These findings will help public health officials develop tools and communication strategies to rapidly address public concerns about vaccine safety as they emerge[272,273].

Research has also shown that a community that is engaged and invested in its immunization program has higher rates of coverage[274–279]. Interventions using strategies that develop community awareness of the importance of vaccines and integrate community members into immunization programs have increased immunization coverage[274–279]. For example, the Global Polio Eradication Initiative (GPEI) found

that in areas where community volunteers participate in polio eradication activities, campaign awareness is higher, fewer parents refuse to give OPV to their children, and there are less missed opportunities to vaccinate[75]. Additionally, they found that when local influential people such as religious, educational, and business leaders in the community endorse polio vaccination and encourage resistant parents to accept OPV for their children, confidence in the safety and efficacy of the vaccine increases[75]. The GPEI also included social mobilization and community engagement in its 2013-2018 Endgame strategic plan, stating that "*poliovirus circulation stands little chance of surviving in fully mobilized communities, even in the most difficult contexts*"[75].

In addition to developing demand for vaccines among community members, advocacy and outreach efforts should also target health care workers, as they are integral to vaccine delivery and have a large impact on both the supply of and demand for vaccines in communities[280–283]. Training programs for local healthcare workers can provide added skills and knowledge to help promote immunization to patients, increasing coverage rates[284]. Many programs have demonstrated how effectively health care workers can encourage reluctant parents to vaccinate their children[285–287].

Public confidence in vaccines and immunization programs is critical to continuing the momentum of current vaccination programs and to providing the benefits of vaccination to the greatest number of people. The NVAC is currently conducting a comprehensive analysis on vaccine confidence and its impact on vaccination programs. Their findings will be detailed in a separate NVAC report.

3. Enhancing global capacity for vaccine safety monitoring and post-marketing surveillance

NVAC Recommendations:

3.1 The ASH should identify mechanisms to encourage ongoing collaborations and technical support between HHS agencies involved in post-licensure vaccine safety, the WHO, and related global agencies and partners to 1) to enhance capacities to build vaccine safety surveillance systems to monitor the safety of vaccines as they are broadly administered; 2) to assess and respond to vaccine safety concerns or signals, effectively communicate vaccine risks; and 3) to support the political will to respond to vaccine safety concerns with evidence based decisions.

Vaccine pharmacovigilance is defined as "*the science and activities relating to the detection, assessment, understanding, prevention and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues*"[288]. The U.S. has a number of vaccine safety monitoring and surveillance systems that serve as models for data collection and epidemiological investigation of the causal links between immunizations and adverse events. For example, the Vaccine Adverse Events Reporting System (VAERS), jointly managed by the FDA's Center for Biologics Evaluation and Research (FDA/CBER) and the CDC's Immunization Safety Office (CDC/ISO), is a post-licensure, spontaneous (passive) reporting system to detect patterns of severe adverse events following immunization (AEFI) in the U.S.[289]. The CDC/ISO also oversees the Vaccine Safety Datalink (VSD), an active surveillance system, which collects and links health outcome data and vaccination registry data from participating managed healthcare databases to assess vaccine safety signals and conduct epidemiological studies to verify the role of vaccination in reported adverse outcomes[290]. These, and other vaccine safety activities that are ongoing in the U.S., have been comprehensively reviewed in previous NVAC reports[291].

Maintaining high public demand for vaccination, and consequently high coverage in communities, is dependent on public confidence in immunization programs and the ability to rapidly detect and respond appropriately to vaccine safety signals. Conversely, a lack of a coordinated vaccine safety system, poor risk communication strategies, or a weak capacity to rapidly conduct scientific investigation in response to real or alleged safety concerns can negatively impact vaccination campaigns and feed misperceptions and fears of vaccines[292–294]. The experience and expertise accrued by HHS agencies through the use of these systems can and should be used by the global community in efforts to optimize intelligence on vaccine safety and to build a global platform for vaccine safety monitoring and communication efforts.

Vaccine Safety is a Global Priority

While infrequent, all vaccines are associated with a risk of adverse reactions. Vaccines undergo stringent safety testing during clinical trials prior to their licensure, but oftentimes the size and composition of clinical trials may not be large enough to capture rare AEFIs or AEFIs that may occur in subpopulations not enrolled in the clinical trials. As vaccines are broadly introduced into the general population, rare AEFIs may become detected. Moreover, vaccine coverage has increased substantially over the past 30 years[70], especially in LMIC that may not have the systems in place to monitor for vaccine safety signals. Therefore, it is imperative to implement global post-marketing surveillance systems that can identify rare, but serious AEFI signals across countries, estimate the rate of incidence of these signals in local

populations, and take action to minimize the potential effects of real or perceived AEFIs on the public and on the immunization system[295].

The growing global demand for vaccines has generated new opportunities for developing countries to actively participate in the development and manufacturing of vaccines, and developing country vaccine manufacturers now produce an increasing majority of the world's vaccine products[296]. However, manufacturers in different countries may have different regulatory standards and capacities than the countries in which the vaccines will be used.

To overcome this challenge, the WHO has created the prequalification process for all UN-procured vaccines. Countries that manufacture vaccines for PAHO and UNICEF procurement must meet WHO prequalification standards for vaccine formulation, manufacturing, and quality control set by the WHO's Expert Committee on Biological Standardization[297]. Manufacturing countries must also have a functional national regulatory authority (NRA) in place that meets key performance indicators determined through a WHO assessment process, including the ability to monitor for AEFIs[298]. The benefits of the WHO prequalification process are two-fold in that it ensures that procuring countries with poorly developed regulatory capacities have access to reliable, high-quality vaccines, while providing a mechanism to strengthen the regulatory capacity in manufacturing countries[299].

Once vaccines have been deployed there remains a continued need to monitor for rare or unexpected vaccine safety signals that only become apparent when vaccines are used among larger populations and groups with more diverse demographics. This is especially true in LMIC where use in immune-compromised populations or populations with other known or yet to be recognized medical conditions may reveal important contraindications[300]. Furthermore, many vaccines that are currently under development such as those targeting dengue, malaria, and tuberculosis are intended primarily for use in LMIC. Enhanced efforts to implement active surveillance for these and other newly-introduced vaccines are needed to determine baselines for AEFIs and refine vaccine recommendations based on safety evidence derived from use in these populations.

The Global Advisory Committee on Vaccine Safety

The WHO Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 as a group of experts that provides the WHO with an independent evaluation of vaccine safety signals and vaccine

safety assessments; enabling the WHO to identify and address global vaccine safety concerns with prompt scientific rigor[301]. The GACVS is comprised of vaccine safety experts from different academic disciplines, sectors, and countries, and has included representatives from the CDC and the FDA. Their professional judgment is consulted in the development of vaccine policy decisions that affect global vaccination programs and strategies. They provide validation of vaccine safety profiles for all WHO prequalified vaccines, assessments of causality for severe adverse events linked in time to vaccines, and judgment in defining high-risk populations and contraindications for vaccines recommended by WHO[295,301]. Similarly, national AEFI review committees may consult with the GACVS for their knowledge and evaluation of vaccine safety signals detected within a specific country or region[301]. In addition, the GACVS improves the accessibility of reliable vaccine safety information for the general public[302].

The GACVS serves as a global forum to discuss new and evolving information on vaccine safety and vaccine safety-related efforts. Though not directly involved in implementing international vaccine safety activities, the GACVS provides the WHO with an independent evaluation of efforts to strengthen global pharmacovigilance and institute standardized approaches to post-marketing vaccine safety surveillance, particularly in LMIC[301]. This includes supporting, through expert input and evaluation, the drafting and implementation of a WHO-led global vaccine safety strategy that provides a detailed "blueprint" for achieving effective vaccine pharmacovigilance systems in all countries. The Global Vaccine Safety Blueprint is discussed in detailed below[303].

International Vaccine Safety Activities – A Landscape Analysis

Before a strategy for achieving global vaccine safety could be conceived, a landscape analysis of existing vaccine pharmacovigilance activities, post-marketing vaccine monitoring capacities, and available resources in LMIC was commissioned by the WHO to provide greater situational awareness of the key barriers to creating an effective global vaccine safety system[304]. The landscape analysis includes a number of studies surveying stakeholder perceptions of the existing processes and procedures, an evaluation of existing systems, and a financial assessment intended to guide global investment priorities[304].

The analysis showed that 65% of WHO member states, including the majority of LMIC, do not have post-marketing vaccine safety monitoring systems in place[304,305]. In many cases, LMIC that primarily procured

vaccines assumed that the producing/exporting countries were monitoring for AEFIs and other vaccine safety issues in the procuring countries as well. In reality, this proved untrue in most cases and highlighted a significant gap in AEFI reporting[304].

These gaps were further exacerbated in many LMIC by the lack of an adequate and empowered national regulatory authority that could respond to potential serious vaccine safety signals[305,306]. Current unmet needs for many countries include a lack of clear mandates to carry out post-marketing surveillance for AEFIs, the legal authority to take action when vaccine safety signals are detected, and regulations and guidelines that establish the roles and responsibilities for vaccine safety between the regulatory authorities, the national vaccine program, and vaccine manufacturers[304]. Regulators in LMIC called for "regulatory mentors" and indicators for post-marketing AEFI surveillance activities included in WHO NRA assessments as mechanisms to strengthen regulatory capacity for vaccine pharmacovigilance[304].

Data collection and information sharing was also a significant challenge identified in the landscape analysis. There was general agreement that a global vaccine safety information database would create opportunities to actively collect, aggregate, analyze, and report vaccine safety data, which could enhance causality assessments and investigations[304]. Yet, an understanding of the types of serious AEFIs and case definitions were found to vary at all levels of the reporting system. Healthcare workers in LMIC sometimes expressed fear or a lack of knowledge to report AEFIs, which could lead to insufficient and incomplete data due to under-reporting of AEFIs[304,307]. Furthermore, a lack of technology infrastructure such as limited computer access and insufficient internet capabilities restricted a country's ability to contribute comprehensive reports[307].

In 2007, the WHO, under the guidance of the GACVS, initiated a pilot project called the Post-Marketing Surveillance Network (PMS Network) to test the ability to create an international platform for strengthening vaccine safety monitoring and stimulate reporting and sharing of vaccine safety data for countries that had recently introduced newly-prequalified vaccines. By 2011, the PMS Network included 12 eligible LMIC half of which reported AEFIs to a centralized database run by the Uppsala Monitoring Center (UMC), the WHO collaborating center for international drug monitoring[307]. Though participation in the PMS Networked enhanced country-level capacity to monitor and report vaccine safety data in general, the results of the pilot project underscored many of the important challenges described above[304].

Finally, the landscape analysis highlighted that very few countries or international initiatives sufficiently addressed vaccine safety risk communications[304]. Access to reliable vaccine safety information, educational materials on the risks and benefits of vaccinations, an understanding of circulating public perceptions, and a well-developed vaccine safety crisis communications plan are all necessary to maintain public trust and participation in vaccination programs[304].

Standardizing Tools to Build Vaccine Pharmacovigilance Capacity in LMIC

Surveys of vaccine safety stakeholders and studies on vaccine pharmacovigilance efforts all cited a lack of harmonized tools such as standard AEFI reporting forms, common databases and compatible information sharing platforms, wider adoption of standard case definitions, and commonly agreed upon guidelines, protocols, and codes of conduct to be major barriers to achieving a truly global vaccine safety support structure[304,305]. A lack of standardized tools within and between countries causes data collected from different countries to be incomparable, limiting its functionality in the aggregation of data for rare vaccine safety signal detection[304]. The use of uniform case definitions and mutually compatible datasets facilitates the ability to conduct international epidemiological investigations by linking multi-country datasets and to communicate consistent scientific information on vaccine safety to decision-makers and the public when serious AEFIs of global concern are suspected[308–310].

The Brighton Collaboration was formed in 2000 as an independent partnership of volunteers to generate, evaluate, and communicate high quality information about vaccine safety through the development of standardized AEFI case definitions and vaccine safety monitoring and assessment tools that could be used universally across settings with diverse expertise and resource availability [311]. AEFI case definitions are comprised of the definitions themselves as well as guidelines for the collection, analysis, and presentation of vaccine safety data developed by AEFI-specific working groups[312]. They are then vetted through a separate reference group of experts before being endorsed and disseminated for public use. Currently, the Brighton Collaboration has developed over 20 standardized case definitions for use in pre-licensure, post-licensure, and post-marketing vaccine safety studies and definitions have been used for both passive and active AEFI surveillance activities (https://brightoncollaboration.org).

Brighton Collaboration AEFI-specific working groups have also developed “bridging tools” such as AEFI-specific reporting forms, checklists, and term glossaries to facilitate uptake and implementation of the

case definitions[313]. The Automatic Brighton Classification (ABC) tool is a specialized software tool that helps standardize AEFI classification based on user-entered information on patient symptoms[314]. Wide-scale adoption and use of these standardized tools by LMIC has the potential to greatly enhance the global impact of vaccine safety monitoring activities.

The Council for International Organizations of Medical Sciences (CIOMS) is also instrumental in creating common vaccine pharmacovigilance terminologies and guidelines[288,303]. Members contribute to, endorse, and disseminate the Brighton Collaboration definitions. CIOMS is a non-profit, international organization formed in partnership between the WHO and the United Nations Educational, Scientific, and Cultural Organization (UNESCO). The CIOMS/WHO Working Group on Vaccine Pharmacovigilance (2005-2011) included international representatives from all sectors to deliberate on consensus definitions and evaluation tools for vaccine pharmacovigilance efforts for use by regulators, national programs, and industry[288,315].

The ability to coordinate linked datasets of spontaneously reported AEFIs and relevant vaccine safety data also provides a powerful tool for detecting and verifying rare or unexpected vaccine safety signals. The WHO also collects spontaneous surveillance information on AEFIs from member countries through the VigiBase database managed by the UMC[316]. Participating countries have the option to use common software to enter vaccine safety information which has been collected through national pharmacovigilance centers, NRAs, and/or national immunization programs. This information is continuously updated and vaccine safety signals are detected through an automated, data-mining signal detection process using a statistical approach to compare the frequency of potential signals to background levels[317]. When a signal is identified, the WHO conducts case evaluations, and if warranted, causality assessments and communicates study findings on individual case safety reports through a periodic newsletter. The UMC also provides guidance for countries wishing to establish a national pharmacovigilance center and assists the GACVS in managing the PMS Network described above[318].

As the Brighton Collaboration has expanded its mission, it now also includes a number of activities that leverage the growing network of partner vaccine safety experts through the use of data safety monitoring boards and large data linkage projects such as the European Vaccine Safety Data Link[319] . Already the Collaboration has established a multi-national partnership of databases with information on over 50 million individuals for vaccine outcome studies.

Building off the Brighton Collaboration, the VaccineGRID is an international health IT platform for linking and sharing healthcare information online from diverse healthcare databases (http://vaccinegrid.org). This partnership allows public health agencies, healthcare organizations, and academics to collaborate on large-scale, hypothesis-driven vaccine safety studies, allowing the quantitation of vaccine effects across populations. Information can be accessed for studies on vaccines and vaccine safety such as meta-analyses, determining incidence rates of AEFIs, comparative effectiveness studies, AEFI signal detection, and quantitative benefit-risk assessments.

Finally, harmonized tools and definitions are effective only if they are understood and utilized properly by personnel trained in vaccine pharmacovigilance activities. WHO provides training modules and learning opportunities for national public health officials, immunization program managers, vaccination staff and members of AEFI review committees through its Global Vaccine Safety Resource Center[320]. The Resource Center includes web-based courses on vaccine safety, training workshops, and vaccine safety training "tool kits" that are intended to build vaccine safety capacity within countries. For example, a "vaccine safety basics" course is available online at www.vaccine-safety-training.org. The resources provided by the Global Vaccine Safety Resource Center are shown in Figure 4 below.

Figure 4. The WHO Global Vaccine Safety Resource Centre Vaccine Safety Training Packages

	Basic Training Needs (remote areas)	Basic Training Needs (requiring direct interaction)	Advanced Training Needs (e.g., AEFI review Committee Members)	National Trainers (advanced training participants)
Global Vaccine Safety Resource Center Available Resources	• E-learning course – Vaccine Safety Basics • Vaccine Safety Basics Training	• E-learning course – Vaccine Safety Basics • Vaccine Safety Basics Training • Vaccine Safety Advanced Training	• Vaccine Safety Basics Training • Vaccine Safety Advanced Training	• Trainer resources

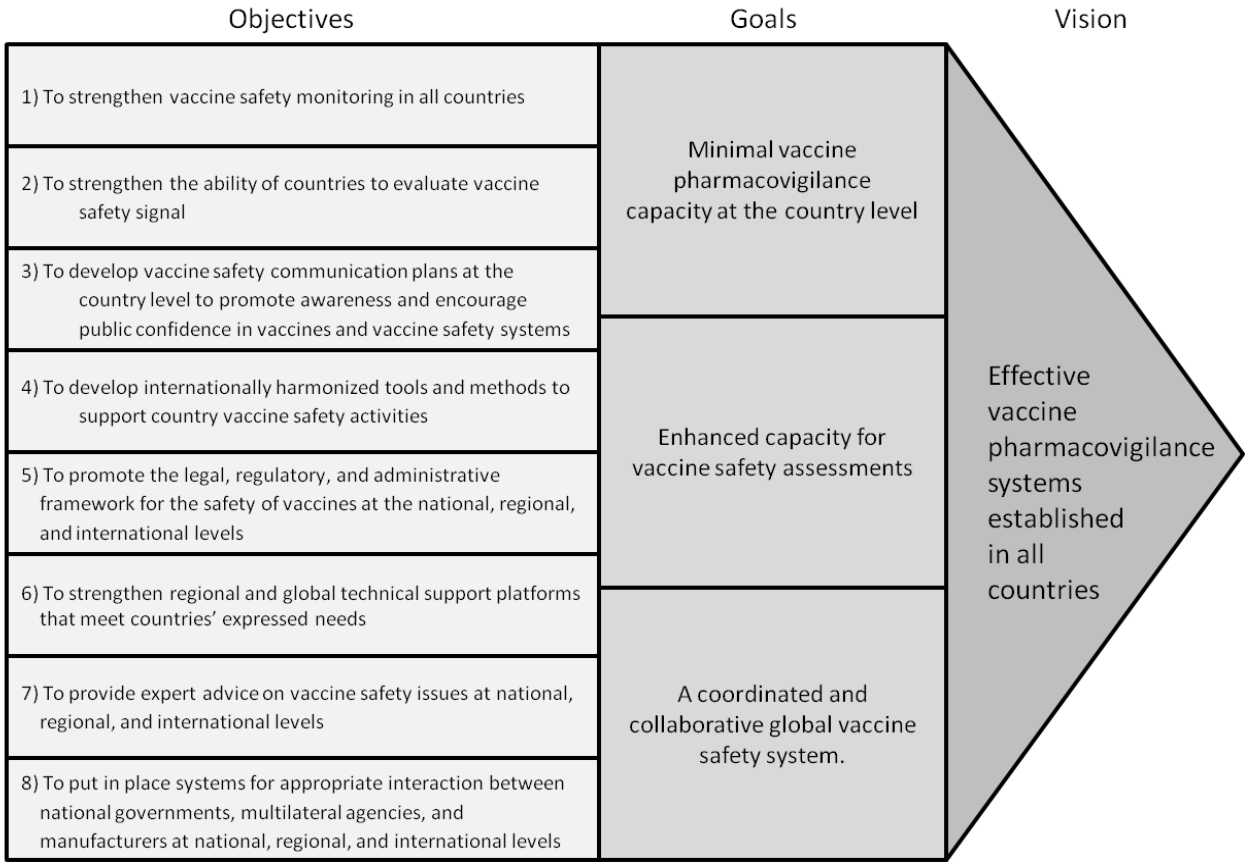
The Global Vaccine Safety Initiative – Blueprint and Implementation

As stated in the Decade of Vaccines Global Vaccine Action Plan, creating greater access to traditional vaccines and introducing new vaccines into LMIC will require an international commitment to coordinating and managing vaccine safety activities[303,321]. The Global Vaccine Safety Blueprint ("the Blueprint") was created to meet this challenge by focusing on overcoming the barriers and gaps in LMIC that were identified in the global vaccine safety landscape analysis and the PMS Network pilot project.

The Blueprint centers on defining three main goals including establishing minimal vaccine pharmacovigilance capacity at the country level, providing enhanced capacity for vaccine safety assessments in countries introducing newly developed vaccines and countries that manufacture and/or use WHO prequalified vaccines, and supporting international coordination and strategic planning to create a collaborative global vaccine safety system. These improved systems will allow for active surveillance of vaccine safety signals, more rapid verification of potential safety signals, scientific investigation of the causal link between vaccines and AEFIs, and better communication of vaccine safety information to decision makers and the public.

The Blueprint is organized into eight objectives that will achieve each of the Blueprint's three overarching goals. The objectives described in the Blueprint are shown in Figure 5 below.

Figure 5. Overview of the Global Vaccine Safety Blueprint



Under each objective, a rationale is provided in the Blueprint that justifies why the objective is included, as well as target indicators for achieving the objective and the expected outputs that will result when the target indicators have been achieved[303].

The Blueprint recognizes that country-level programs will require varying levels of international assistance (both financial and technical) to implement the strategies described, especially as new vaccines are introduced into national immunization programs. To guide its implementation, the WHO has created the Global Vaccine Safety Initiative to coordinate international vaccine safety activities and allow a forum for discussion and input from the GACVS and other immunization experts[307].

The Global Vaccine Safety Initiative is charged with creating a global vaccine safety support structure and includes a detailed work plan for implementing and achieving the vision outlined in the Blueprint[322]. The work product portfolio currently includes more than 80 proposed or on-going vaccine safety capacity-building activities that are periodically evaluated and prioritized based on their potential impact, the degree of change they will implement, future uses, and if they are stand-alone or enabling activities[323]. Based on these criteria, projects are given a priority for current and future funding. Detailed descriptions of the different international vaccine safety activities improve visibility of ongoing efforts, preventing duplication or overlap, and facilitating allocation of resources. The product portfolio will be used as a management tool to track progress and mark milestones of activities under the eight objectives outlined in the Blueprint[323,324].

HHS Activities to Promote Global Vaccine Safety Monitoring

As mentioned previously, vaccines are used world-wide and the ability to detect and communicate rare and serious vaccine safety signals is a priority for all nations. HHS participation in these initiatives will help to achieve stronger vaccine safety surveillance both within the U.S. and abroad. The CDC participates through its Immunization Safety Office and FDA/CBER has established the Global Regulatory Utilization of Vaccine Safety Surveillance Initiative to coordinate their respective roles in vaccine safety capacity building activities.

Experts from both CDC/ISO and FDA/CBER have been called upon to serve as representatives on a number of WHO advisory committees including the GACVS, the Strategic Advisory Group of Experts (for vaccines and immunizations), and the Expert Committee on Biological Standardization. FDA/CBER and

CDC/ISO also participate as a member of CIOMS and have contributed to reports issued by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance described above. CDC/ISO and FDA/CBER also provided input and feedback on the WHO's Global Vaccine Safety Blueprint and will continue to actively participate in the Global Vaccine Safety Initiative through pilot projects, evaluations, and assistance in prioritizing portfolio activities.

CDC/ISO and FDA/CBER are actively involved in global efforts to standardize vaccine safety case definitions and create harmonized tools for better AEFI detection and response. Both support the Brighton Collaboration by reviewing manuscripts and case definitions as part of the AEFI working groups and downstream reference groups. CDC hosts international scientists from LMIC to train with experts in the CDC/ISO in the development of AEFI surveillance systems. CDC/ISO also assists WHO in hosting causality workshops and development of causality toolkits to help countries better assess vaccine safety signals that have been detected through passive and active vaccine safety surveillance systems.

As part of the Global Research in Pediatrics-Network of Excellence (GRiP Network) (www.grip-network.org/), CDC/ISO and FDA/CBER have collaborated with the UMC in comparing pediatric AEFIs reported to VAERS and reports sent to Vigibase. Results from these studies are being used to optimize data integration and hone global AEFI signal detection. This pilot project will serve as a foundation for follow-on collaborations with UMC. Similarly, CDC/ISO and FDA/CBER participated in an international study to assess the risk of Guillan-Barré Syndrome following influenza A (H1N1) 2009 pandemic vaccines[325].

Moreover, CDC/ISO and FDA/CBER support global vaccine safety capacity building through participation in the development of a Pan American Vaccine Safety Network. Efforts include the formation of a regional committee on vaccine safety, implementing pilot projects to strengthen vaccine safety monitoring, and developing activities focused on crisis prevention and management[326]. FDA/CBER also functions as a PAHO/WHO Collaborating Center for Biological Standardization.

As part of its mission, FDA/CBER works with the global community to increase regulatory capacity through training, sharing of best practices, and serving as a WHO reference NRA for eight pre-qualified vaccines. Many LMIC are limited in their abilities to successfully implement vaccine pharmacovigilance activities because of insufficient regulatory capacity. In 2012, FDA/CBER awarded a cooperative

agreement grant to the WHO to support innovative approaches to vaccine clinical trial design, utilization of pharmacovigilance tools, and scientific collaboration in pharmacovigilance to advance global access to safe and effective vaccines. An example of these activities includes evaluating the use of social media and mobile communication devices for gathering public health information from low and middle income countries[327]. FDA/CBER also collaborates with WHO to host seminars and workshops for sharing methods used by FDA/CBER scientists to assess post-marketing safety data and inform subsequent regulatory actions taken for vaccines and other biologics. For example, FDA/CBER collaborated with USAID and others to provide a comprehensive evaluation of regulatory capacity in sub-Saharan Africa[328] and hosted workshops in these countries to provide guidance on how to design strategies that apply a systems perspective to strengthening vaccine pharmacovigilance.

4. Building Global Immunization Research and Development (R&D) Capacity

Vaccine research and development (R&D) is a global enterprise. Scientific discovery and innovations in immunization technologies, vaccine production, and regulatory science benefit all populations by creating greater access to disease prevention tools and new avenues for product development. Advances in vaccinology are allowing the global community to overcome challenges to vaccine development and extend the benefits of immunization to new target populations. Also, innovative collaborations between the public and private sectors are leading to more efficient approaches to vaccine R&D and manufacturing. This is expanding the global capacity to develop, produce, and deliver vaccines for known infectious diseases and those that may emerge.

Yet, the potential impact that vaccines could have on public health has yet to be fully realized. Effective vaccines are still not available for numerous infectious diseases of global concern such as HIV and malaria. Advances in these areas will require ongoing support of scientific research to identify new antigenic targets, better understand the immune response, and move novel vaccine platform technologies forward. Research into the implementation of immunization programs can also elucidate factors that affect access and public demand for vaccines and immunization services, as well as highlight the scientific, technical and market barriers that may impede continued progress in vaccine development, manufacturing, and delivery.

The NVAC recognizes HHS's leadership in vaccine and immunization R&D and the interdependence between domestic and global efforts in these areas. The collective expertise provided by HHS agencies

should be utilized to strengthen and expand vaccine and immunization R&D capacity in many countries. These efforts will increase the likelihood that vaccine candidates and evolving technologies will be identified, tested and evaluated, accessed, and used by the global community. As a result, a robust global capacity for vaccine development and manufacturing will create a world that is better prepared to respond to and protect against new or evolving infectious disease threats more quickly and more efficiently.

Basic Research: The building blocks for vaccine discovery, development, and delivery

NVAC Recommendation

4.1 The ASH should support efforts that increase global health research capacity through partnerships between health research institutions in the U.S. and abroad. These partnerships create opportunities to train the next generation of U.S. and foreign scientists to better address current and future global health needs, including the development and evaluation of new vaccines, new vaccine delivery systems, country-specific immunization schedules, and new technologies that facilitate global immunization efforts.

In the past 30 years, basic scientific discovery has been instrumental in creating opportunities for new vaccine development. Breakthroughs in the fields of genomics, bioinformatics, molecular biology, proteomics, and biophysics now make it possible to take a directed approach to identifying and verifying vaccine targets[329]. Infectious disease research has led to a better understanding of the molecular characteristics of pathogens and how specific antigens lead to disease pathologies. Systems biology approaches have helped to elucidate the complex interactions between vaccine antigens and the host immune response[330].

Furthermore, the expanding repertoire of molecular tools presents a growing number of technologies that serve as development platforms for new and future vaccines. Recombinant protein expression systems[331,332] and conjugation technologies[333] have made it possible to develop safer, more effective vaccines against a number of once intractable infectious diseases. These technologies are undergoing further refinement to optimize their efficiency and utilization for developing vaccines against new targets such as bacterial pathogens and other emerging infectious disease threats[331,332]. Promising platform technologies such as DNA vaccines are still under development. Although none are currently licensed for use in humans, DNA vaccine technologies have the potential to open entirely new avenues

in vaccine development[334]. A number of DNA vaccines have entered clinical trials, including dengue vaccine candidates. Finally, there is considerable interest in using adjuvants as a tool to improve the effectiveness and equitable distribution of vaccines to the global market[335,336]. Adjuvants can increase the benefits of vaccines to broader patient populations by stimulating seroconversion in typically hypo-responsive individuals such as the elderly, immune-compromised patients, and non-responders[337,338]. Importantly, studies indicate that adjuvants boost the effectiveness of antigens, allowing less antigen to be used per dose, thus maximizing vaccine supplies when needed to meet sudden global demands, such as during an influenza pandemic[339].

Vaccine delivery technologies that have directly benefited Low and Middle Income Countries (LMIC)

Advances in vaccine technologies have not only led to the discovery and development of new vaccines, they have also made vaccine delivery safer and more efficient. Innovations are overcoming many of the logistical barriers immunization programs face in developing countries due to limited human resources, weak supply chains, and fragile health systems. Continued efforts towards developing new vaccine delivery technologies will optimize and strengthen routine and supplementary immunization activities. Examples of vaccine delivery technologies that have already expanded access to safe and effective immunization programs are described below.

Needle-free vaccine delivery systems

In 1999, a systematic review of injection safety in developing countries found that a significant number of injections were deemed unsafe in such countries mainly due to the improper re-use of disposable syringes[340]. Importantly, poor adherence to safety protocols caused increased transmission of blood-borne pathogens in these countries[340] prompting UNICEF to implement procurement policies that require auto-disable syringes (a.k.a., auto-disposable syringes or reuse prevention syringes) for vaccines delivered via routine and mass immunization programs[341]. Now, new strategies to minimize the risks associated with unsafe injection practices involve the development of needle-free delivery systems including aerosolized vaccines, jet injectors, and microscopic arrays called microneedles [342–346]. Because they do not utilize needles and syringes, needle-free technologies reduce biohazardous waste, minimize the risks of accidental needle-sticks, and prevent the re-use of disposable materials that can lead to the transmission of blood-borne pathogens between patients**.** They may also require less training of personnel for delivery indicating that a greater number of vaccines could be deployed during vaccine

campaigns[343,345]. Lastly, needle-free systems can also alleviate fears related to injections, creating the potential for higher acceptance and better completion within populations[347].

Thermostable vaccines

Cold chain systems have been established to ensure that vaccines are kept at optimal temperatures at each stage of the supply chain until they reach their target populations. However, in many developing countries poorly functioning equipment, frequent power outages, variations in cold chain needs by product, and the need for better training in cold-chain requirements can often expose vaccines to improper temperatures. Vaccine storage and transport is a growing concern as the incorporation of new vaccines into national immunization programs can stress already fragile vaccine supply chains[348]. Solutions have included research to make existing vaccines more stable and potent outside of the standard cold chain temperature range, developing lyophilized (dry) vaccine formulations and advanced processing technologies to improve stability, and developing novel vaccine stabilizers that can withstand unfavorable temperature conditions[349]. Recent promising innovations in vaccine thermostabilizing agents have included the use of silk matrices to stabilize vaccine antigens at temperatures up to 60°C (140°F) for up to six months[350].

Future research needs

Scientific discovery is delivering promising new vaccine candidates, tools, and technologies to take on seemingly intractable infectious diseases such as HIV, malaria, tuberculosis, and dengue. Progress is also being made in gaining a greater understanding of emerging infectious diseases and neglected diseases and their impact on global populations. Despite these encouraging steps forward, important knowledge gaps remain. In some cases, this includes a basic understanding of pathogenesis, host-pathogen interactions, the role of specific antigens in eliciting a protective response, or a better understanding of how findings in animal models correlate with human disease.

The immune response to vaccine preventable diseases is not always well-characterized. Better understanding of the host immune response, correlates of protection, and impacts of the environment, genetics, age, and other factors on vaccine efficacy and safety are all needed to guide vaccine development efforts, advance candidates through the development pipeline, and direct post-marketing safety surveillance efforts[351].

Global immunization programs would also benefit from advances in operations and implementation research to identify and overcome barriers to routine immunization and the introduction of new or underutilized vaccines. Currently, the WHO is conducting a comprehensive assessment of the recommended childhood vaccine schedules at the global and country-levels to identify epidemiological, social, and economic considerations for optimizing national vaccine programs based on local circumstances and data. Likewise, studies to assess immunization program effectiveness and best practices will facilitate the development of tools and strategies to best meet the health needs of developing countries[352].

Finally, interdisciplinary approaches will be necessary to create novel strategies for tackling vaccine-preventable diseases. For example, the One Health Initiative facilitates interdisciplinary collaborations to better understand and address the interconnectedness of human and animal health and the health technologies that can benefit both (www.onehealthinitiative.com). These efforts are advancing the discovery and development of vaccines for existing and emerging zoonotic diseases. Following the 1999 emergence of West Nile Virus in the U.S., simultaneous efforts were launched to develop vaccine candidates for both humans and horses using a live chimera vaccine technology originally developed for Japanese Encephalitis Virus vaccine candidates (ChimeriVax™)[353]. With funding from the NIH, vaccine developers utilized a functional backbone of the attenuated yellow fever virus, YFV 17-D, to express structural antigens from the West Nile Virus[353]. In 2006, the West Nile virus live flavivirus chimera vaccine was licensed by the USDA for use in horses under the trade name PreveNile™. While a West Nile Virus vaccine candidate was not further pursued in humans, this technology has been applied to the development of other human vaccines, including vaccine candidates for dengue virus [354,355].

Building Capacity in Developing Countries through Scientific Collaboration

In 2011, NIH funded approximately US $1.7 billion in vaccine-related research (total of all research activities)[356]. Though primarily supported through the National Institute of Allergy and Infectious Diseases (NIAID), multiple NIH institutes support research projects on all aspects of vaccines, immunizations, and global health. In general, NIH-funded research benefits the global community by creating knowledge that can be universally applied to global health problems. For instance, NIH was identified as the single largest funder of neglected disease research, accounting for a third of the total global support in 2009[357]. More directly, NIH supports researchers in low and middle income countries by helping them obtain the tools, resources, and networks to tackle their own priority health issues.

The NIH's Fogarty International Center (FIC) focuses exclusively on supporting global health research carried out by both U.S. and international scientific investigators and promotes advancing global health by "taking science to where the problems are" [358]. FIC, in collaboration with other NIH institutes, has supported over 5,000 scientists in LMIC in investigator-led research and research training programs[359], and each year over 2,500 scientists from outside of the U.S. work within intramural NIH laboratories on a number of global health issues. Moreover, the Fogarty International Research Collaboration Award has provided over 450 grants to support international research partnerships, and approximately 20% of Fogarty awards are granted directly to research institutions in LMIC[358]. These types of collaborations ensure that all populations continue to benefit from cutting edge science and innovations to solve problems related to health and disease.

The Indo-US Vaccine Action Program

Since 1987, the U.S. has partnered with the government of India to form the Indo-U.S. Vaccine Action Program (Indo-U.S. VAP). This bilateral collaboration includes broad support for vaccine-related research and innovations including laboratory-based research, epidemiological studies, field trials, vaccine quality control, and vaccine delivery[449].

The Indo-U.S. VAP has awarded over U.S. $10 million, matched in Indian rupees, to more than 60 collaborative projects involving U.S. and Indian researchers from both academia and government. This fruitful collaboration has produced ~300 publications in peer-reviewed journals[450]. In addition, the program has sponsored more than 30 workshops and expert consultations on vaccines and infectious diseases[450].

Early Indo-U.S. VAP projects have included the development of a rabies vaccine, a typhoid vaccine, and most recently a rotavirus vaccine. The rotavirus vaccine, marketed under the trade name RotaVac™ is a notable achievement. When licensed, it will be the first vaccine developed completely in India[451]

Vaccine Research and Development (R&D) Capacity – Strategies to bring forth the next generation of vaccines

NVAC Recommendations

4.2 The ASH should encourage HHS agencies to work closely with USAID, WHO, end-users (including national immunization program managers, Ministries of Health, National Immunization Technical Advisory Groups (NITAGs)), and vaccine manufacturers to support WHO in their efforts to define vaccine target product profiles.

4.3 The ASH should support NIH and FDA ongoing efforts to communicate strategies for minimizing barriers to the development of vaccine products. These efforts enhance the identification, testing, and evaluation of promising vaccine candidates to ensure candidate vaccines advance more quickly through the development pipeline.

Despite many important scientific advances, the vaccine development pipeline continues to be challenged by high risk and rising costs. The majority of vaccine candidates do not progress successfully through the product development pipeline, and studies suggest that technologically complex targets and increasingly stringent regulatory requirements contribute to high rates of attrition[360,361].To counter R&D costs, developers have previously focused on vaccines that primarily meet the demands of high-priced markets, which were more likely to generate a sufficient return on investments[362]. For example, in 1993 vaccine sales in high income countries made up only 12% of the global volume, yet generated 82% of the total revenue[363]. Now, new strategies are being utilized to stimulate R&D efforts for less lucrative vaccines that are specifically intended to address the needs of developing countries. These include establishing clear vaccine priorities, providing resources to support product development partnerships, and providing technical assistance to facilitate the progression of products through the development pipeline.

Setting and Communicating Vaccine R&D Priorities

Vaccine developers need to know that their products will be met with sufficient demand and a supportive policy environment in order to rationalize their investments. Yet, epidemiological considerations, economic considerations, public health awareness, and demand for vaccines can vary significantly across countries. Decision-makers can guide R&D efforts by specifying vaccine priorities based on comprehensive evaluations of the local need and the capacity to incorporate the new vaccine into the existing national health system. For developing countries with limited resources and health infrastructure, setting vaccine priorities may also help to advocate for greater resource allocation by donor organizations, NGOs, policy-makers, and industry partners.

The Decade of Vaccines Global Vaccine Action Plan does not outline a list of global vaccine R&D priorities in recognition that these priorities may be country-specific. However, the WHO Initiative for Vaccine Research Strategic Plan (2010-2020) was developed to establish a global research agenda to guide WHO and others in developing research priorities, standards, and guidelines and incorporating research results into policies and practice[352]. The priority areas discussed in the plan emphasize WHO's role in convening global stakeholders and facilitating the involvement of developing countries in these efforts[352].

The HHS National Vaccine Program Office (NVPO), in collaboration with the Institute of Medicine, is supporting the development of a software tool that can assist in prioritizing vaccine development efforts. The Strategic Multi-Attribute Ranking Tool for Vaccines (SMART Vaccines) software prioritizes vaccine products based on attributes chosen and weighted by the user[364]. Attributes span broad categories such as disease burden, business opportunity, economic considerations, demographic considerations, scientific/technical considerations, public concerns, programmatic considerations, and policy considerations[364]. The resulting ranked list of vaccines can then be evaluated by stakeholders using a common and transparent platform for discussion.

Stakeholders can also communicate vaccine priorities to the R&D community through the formulation of target product profiles (TPPs), which serve as technical strategies for achieving the characteristics that a vaccine should possess in order to maximize its adoption by end-users[365] (see Appendix B for an example of a TPP). These attributes are usually defined through preliminary assessments at the national level of the need, demand, cost-effectiveness, and feasibility of delivering the desired vaccine. A TPP may specify characteristics such as target pricing, efficacy, or age-range of the population intended for the intervention. TPPs can also be used to formulate clinical research questions that may generate data to answer future policy questions related to the vaccine and its use[365]. For example, a TPP was established as part of the Advanced Market Commitment strategy employed in the development of pneumococcal conjugate vaccine for use in Africa and Asia (November 2007 SAGE meeting, Session: Pneumococcal Conjugate Target Product Profile)[366].

Product Development Partnerships

Product development partnerships (PDPs) have played a major role in stimulating R&D activities for vaccines by uniting resources and efforts across academia, NGOs, and the public and private sectors towards achieving a common technological goal. PDPs may also stimulate the market by drawing attention to the prevalence or importance of a public health problem. One study noted that government funding of PDPs through agencies such as USAID and the UK Department of International Development increased from 7% of their total support in 2000 to 34% in 2007[219]. Consequently, these investments encourage the participation of new players in the R&D process[367].

PDPs divide the development process into segments, which can be addressed through the expertise of the individual partners. For example, NIH assists both individual investigators and development partners in evaluating potential vaccine candidates early in the development process by assisting in feasibility studies and providing preclinical and clinical services[368]. In addition, both NIH and FDA assist development partners in identifying and planning for moving a candidate product through different phases of the development pipeline.

The coordination of resources and technical expertise allows the PDPs to pursue a portfolio of more innovative, high-risk projects, including vaccines and technologies that the private sector might not otherwise pursue [369]. In addition, the PDP portfolio approach can reduce the time needed to bring a vaccine to market by pursuing a number of promising candidates in parallel.

NIH's Vaccine and Treatment Evaluation Units and the HIV Vaccine Trials Network

NIH/NIAID supports the development and testing of vaccines both within the U.S. and globally through its network of Vaccine and Treatment Evaluation Units (VTEUs)[452]. Established since 1962, these sites carry out clinical studies and trials spanning a wide spectrum of infectious diseases. The scope of the VTEU's work is being expanded to encompass studies in international populations, including in resource-poor settings and in populations with diseases endemic to the specific location.

Internationally, the NIH/NIAID also supports the HIV Vaccine Trials Network (HTVN), a consortium of leading researchers across 27 cities in four continents all focused on developing a safe and globally effective vaccine to prevent HIV/AIDS. The HVTN works together to optimize clinical trial designs to test and evaluate HIV vaccine candidates on safety, immunogenicity, and efficacy[453].

To date, one of the most successful vaccine PDPs has been the Meningitis Vaccine Project. Global efforts to control group A meningococcus (Men A) were ignited following a massive outbreak in sub-Saharan Africa's "meningitis belt" region[219]. The limited market and pricing requirements (≤$US 0.50 per dose) for a potential vaccine were among the factors prompting the formation of the Meningitis Vaccine Project as a partnership between the WHO, PATH, and the Bill & Melinda Gates Foundation to accelerate vaccine development [219]. The technology to produce the vaccine was developed by FDA's Center for Biologics Evaluation and Research (FDA/CBER) and transferred to the Serum Institute of India, Ltd for manufacturing[370]. Working through the National Regulatory Authority (NRA) of India, the vaccine was licensed in 2009 under the name MenAfriVac® and earned prequalification status by the WHO in 2010[219]. By December 2012, through significant support from GAVI, 100 million doses of MenAfriVac® were administered in 10 countries[371] and preliminary evidence suggests MenAfriVac® has already had a significant impact on bacterial transmission in vaccinated communities[372].

In 2000, a study analyzing the global burden of pneumococcal disease estimated that 826,000 deaths occurred in children less than five years of age, with 95% of these occurring in Africa and Asia[162]. Following the 2000 study, a broad coalition of international partners, including The Gambian government and the British Medical Research Council, NIH/NIAID, the London School of Hygiene and Tropical Medicine, WHO, USAID, CDC, Wyeth-Lederle Vaccines, and PATH partnered to conduct pneumococcal vaccine trials using conjugate vaccine containing nine of the pneumococcal serotypes most common in The Gambia[373]. Findings from this study indicated that vaccinating infants with pneumococcal vaccines could substantially reduce death and illness from pneumococcal infections[373]. In 2010, the FDA partnered with PATH to advance the development of a low-cost pneumococcal vaccine using conjugation technologies developed by the FDA, as was used for the meningococcal vaccines[374]. Following successful adaptation of the technology in May 2012, FDA scientists trained staff from the China National Biotec Group's Chengdu Institute of Biological Products for five weeks in FDA laboratories to perform the procedure and transfer the technology at no cost.

Pneumococcal Advanced Market Commitments

In contrast to the PDPs which focus on supporting the R&D process, the Advanced Market Commitment (AMC) approach has been proposed as an alternative strategy to provide incentives for vaccine manufacturers by creating markets through long-term advanced purchase commitments of vaccines at set prices and quantities once the vaccines have been developed.

UN agencies, working closely with GAVI and the governments of developing countries, procure vaccines developed by the manufacturers at a pre-agreed set price[454]. Donor funds are then used to supplement manufacturers to offset the fixed costs incurred in the R&D process[455]. Once donor funds are depleted, vaccine manufacturers are committed to continue providing a set volume of vaccines at a set price for the duration of the commitment (e.g., 10 years).

During this time, GAVI progressively transfers the costs of vaccines to developing countries to ensure that the governments of developing countries create sustainable budget plans for vaccines once the AMC is fulfilled and market forces are in play[454].

As a proof of concept, the Pneumococcal AMC was implemented in 2009 for the development and delivery of pneumococcal vaccines for developing countries. The AMC was supported by donor funds from the Bill & Melinda Gates Foundation and the governments of the United Kingdom, Italy, Canada, Russia, and Norway. Working with vaccine manufacturers, GAVI began introducing pneumococcal vaccines into eligible countries in 2010[454]

Since 2010, GAVI has facilitated the introduction of pneumococcal vaccines to 18 eligible countries and plans to immunize 90 million children with pneumococcal vaccines in more than 50 GAVI-supported countries by 2015[454].

Other examples of PDPs with vaccines currently under development include:

- *The PATH Malaria Vaccine Initiative (http://www.malariavaccine.org)*
- *Dengue Vaccine Initiative (http://www.denguevaccines.org)*
- *AERAS Global Tuberculosis Product Development Organization (http://www.aeras.org)*
- *The International AIDS Vaccine Initiative (http://www.iavi.org)*

Future product development partnerships may also be utilized for the development of vaccines with improved delivery mechanisms, greater effectiveness, lower costs, or as part of combination vaccines.

Harmonizing Regulatory Standards to Support Global Vaccine Development

NVAC Recommendation

4.4 The ASH should support efforts to strengthen national regulatory authorities in other countries through collaborations with the FDA. The ASH should support on-going FDA efforts with other National Regulatory Authorities and the WHO to continue seeking opportunities to inform, shape, and communicate global regulatory standards and requirements for the development and manufacturing of safe and effective vaccines. In doing so, HHS will continue to strengthen international programs including building and strengthening global regulatory capacity and quality systems.

Ongoing international collaborations to standardize clinical trial guidelines and strengthen regulatory capacity in developing countries can help minimize the financial and logistical burden on both manufacturers and regulatory authorities. The use of standardized tools and procedures can also strengthen the capabilities of existing regulatory authorities, provide guidance to those just starting to establish regulatory capacity, and promote transparency of the regulatory process between manufacturers and regulators[375].

Global harmonization of regulatory standards

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was formed in 1990 as a collaboration between regulatory authorities and industry leaders in the U.S., Europe, and Japan. The ICH works to align technical requirements for reporting and evaluating data on quality, safety, and efficacy of new medicinal products[376]. These efforts include establishing common data requirements and implementing compatible data submission formats for investigational new drug (IND) applications to minimize the redundancies and inefficiencies experienced by vaccine manufacturers when submitting applications to regulatory authorities in multiple regions[377]. For example, the ICH developed a “common technical document” to harmonize the documentation needed for a new drug application among the three ICH regions. This platform saves both time and resources by providing a common electronic format for

documenting and submitting technical data requirements and allowing vaccine manufacturers to simultaneously submit IND applications to multiple ICH regions[375,377]. The common technical document also benefits regulatory agencies by facilitating the exchange of information during the review process[375].

As interest in harmonizing regulatory practices has grown, ICH has linked its efforts to the broader global community by establishing a Global Cooperation Group (ICH GCG). Members work closely with the WHO and other international organizations to share information about ongoing regional harmonization efforts and to facilitate the adoption and implementation of ICH guidelines regionally and globally[375]. The ICH GCG includes representatives from five regional harmonization initiatives (Asia-Pacific Economic Cooperation , the Association of Southeast Asian Nations, the Gulf Cooperation Council, the Pan American Network for Drug Regulatory Harmonization, and the Southern African Development Community) and focuses on providing tools and resources for participating members[375].

Though not limited to vaccine development, the ICH has developed standardized guidelines for a number of regulatory issues relevant to the evaluation of vaccine quality, safety, and efficacy. As such, representatives from FDA/CBER participate as members on the ICH's Steering Committee and FDA works closely with the ICH to promote regulatory harmonization as part of its strategic objectives for improving global public health through international collaboration including research and information sharing (FDA/CBER Strategic Plan 2012-2016, Goal 2)[378].

Building Regulatory Capacity in Developing Countries

Ensuring that national immunization programs can consistently deliver vaccines that have passed high quality and safety standards is paramount to protecting global health. In 1987, the WHO implemented the prequalification program requiring that all UNICEF and PAHO procured vaccines meet the standards for vaccine formulation, manufacturing, and quality control set by the WHO's Expert Committee on Biological Standardization[297]. To date, 27 manufacturers in 21 countries have achieved prequalification status[379]. Prequalification also requires countries that manufacture prequalified vaccines to have a functional national regulatory authority (NRA) in place that meets key performance indicators determined by a WHO assessment process. However, an analysis by the WHO (1997-2007) found that only 58 out of 193 Member countries had functional NRAs[380]. Importantly, several countries where

clinical trials were planned were found to have inadequate regulatory capabilities or technical expertise to competently evaluate vaccine clinical trial protocols[381].

The WHO's Developing Country Vaccine Regulators Network (DCVRN) was established in 2004 in order to strengthen the national regulatory authorities (NRAs) of countries with emerging vaccine manufacturing capabilities[382]. These countries include Brazil, China, Cuba, India, Indonesia, the Republic of Korea, Russia, South Africa, and Thailand. Convened annually, the DCVRN offers NRA representatives of member countries the opportunity to build consensus on standards, voice gaps in regulatory competencies, discuss best practices for evaluating clinical trials, and identify areas for increased coordination with more established NRAs (such as the FDA)[382].

The original emphasis for DCVRN efforts focused on developing competencies to authorize, monitor, and evaluate vaccine clinical trials. However, discussions now also include information on new vaccines, vaccines in development and post-marketing issues following vaccine introduction. Their accomplishments include the development of common methodologies and procedures such as a checklist for Good Clinical Practices (GCP) inspections and the implementation of an IND-like system for NRAs in developing countries (piloted in Brazil and Indonesia)[383]. Their efforts have also highlighted the need for NRAs to establish formal mechanisms to interact with national immunization technical advisory groups (NITAGs) for better communication regarding the scientific evidence of disease burden, vaccine safety and effectiveness, and potential off-label uses[384].

The WHO also identified important regulatory gaps in African countries that did not produce vaccines, but had been designated to host large, multi-center vaccine clinical trials. In response, the African Vaccine Regulatory Forum (AVAREF) was established in 2006 as part of regional efforts to provide regulatory expertise and training to these countries. The AVAREF convenes biannually and includes representatives from the NRAs, ethics committees, and scientific advisory committees of 19 African countries. Similar to the DCVRN, their efforts are focused on promoting communication and collaboration between Member countries and cooperating partners such as the FDA, the European Medicines Evaluation Agency, PATH, and the European and Developing Countries Clinical Trials Partnership[381].

AVAREF representatives have collaborated with WHO, vaccine manufacturers, and clinical trial sponsors to conduct joint reviews of clinical trial applications and clinical trial site inspections. Joint reviews and inspections include all countries currently selected for clinical trials, as well as those targeted for future clinical trial sites. These efforts streamline the approval of clinical trial applications, while strengthening the regulatory capabilities in the participating countries[385]. Moreover, joint evaluations give regulators and ethics committee members the opportunity for a more complete understanding of ethical and scientific considerations required when reviewing clinical trial applications and implementing GCP. It has also created better understanding, and in some cases formalized, the roles and responsibilities of both the NRA and national ethics committees in the clinical trials evaluation process[385].

FDA/CBER works closely with these types of organizations to provide technical assistance and strengthen global regulatory capacity. FDA/CBER supports the DCVRN through a recurring Foreign Regulators Seminar that provides opportunities for sharing of FDA practices and procedures via face to face and web-based interactions. For example, WHO and FDA hosted a training workshop for the Thai NRA intended to strengthen their regulatory capabilities to perform independent evaluation of marketing authorization applications for Japanese Encephalitis vaccines. These workshops improve information sharing and work to create a greater network of regulator expertise for LMIC to consult when planning regulatory capacity-building activities. Similarly, FDA/CBER supports the AVAREF by providing technical support for implementing IRBs, attending annual meetings as expert advisors, interacting with ethics committees, conducting joint reviews and clinical trial site inspections, training in adverse event monitoring, and providing advice on how to carry out vaccine clinical trials using global GCP standards.

The Emergence of Developing Country Vaccine Manufacturers

NVAC Recommendation:

4.5 The ASH should support HHS agencies in their efforts to develop training modules and workshops for vaccine manufacturers in developing countries on best practices and approaches for vaccine manufacturing and Good Manufacturing Practice (GMP) guidelines.

Traditionally, multinational pharmaceutical companies have dominated the market with 70% of revenues generated from the sale of vaccines in high income countries[386]. However, vaccine manufacturers in developing countries are now emerging as competitive players in the global vaccine

market. In-country or regional manufacturing of vaccines provides the advantage of manufacturers working closely with national immunization programs to focus production on vaccines that meet the endemic public health needs, as well as the regulatory standards, of that country[387,388]. Importantly, the increased number of developing country vaccine manufacturers involved in vaccine production contributes to overall supply of quality vaccines, thereby driving down costs and opening markets to a greater range of developing countries [388]. In addition, broader distribution of manufacturing sites improves the global capacity to provide vaccines, decrease the possibility of vaccine shortages, and creates better surge response capabilities that could be leveraged during an influenza pandemic[339].

Developing Country Vaccine Manufacturers Network

The Developing Country Vaccine Manufacturers Network (DCVM Network) was formed in 2000 as an alliance ‘‘to provide a consistent and sustainable supply of quality vaccine at an affordable price to the entire globe”. Organizations such as WHO, HHS, and USAID provide technical support to aid in these efforts that may ultimately lead to achieving WHO pre-qualification status [387]. The DCVM Network now consists of 38 members, eight members of which are WHO Prequalified, enabling the DCVM Network to supply the majority of vaccines purchased by UNICEF and PAHO[387,389]. It is estimated that two-thirds of the world’s children now receive at least one vaccine that was produced by a manufacturer in a developing country[389].

The success of these emerging markets has led to collaborations that utilize the collective strengths of the DCVM. Significant contributions from the DCVM Network expanded the production of prequalified pentavalent vaccines (DTP-HepB-Hib), lowering the price per dose and creating a mechanism for GAVI to better incorporate these vaccines into their programs[388]. Now, the global community is leveraging the DCVM Network to augment domestic and regional vaccine manufacturing to maximize vaccine production capacity in the event of an emerging infectious disease of global public health importance such as pandemic influenza.

Global Vaccine Production Capacity as a Key Strategy in Influenza Pandemic Preparedness Efforts

In 2006, the WHO convened a meeting of subject matter experts to address concerns over the impact of insufficient vaccine supplies on influenza pandemic preparedness efforts. An analysis by the WHO revealed that global production capacity for seasonal influenza vaccines fell several billion doses below the number needed to protect the world in the event of a severe influenza pandemic[390]. Notably, 90% of

the world's population do not reside in countries with influenza vaccine manufacturing capacity, and would most likely suffer from restricted access to the vaccine in the event of a pandemic. The WHO concluded that protecting these populations would require strategies to expand seasonal and pandemic influenza vaccine production capacity in vulnerable countries[390]. The Global Action Plan for Influenza Vaccines (GAP) was developed to address these concerns.

As part of the action plan, the WHO, in collaboration with the HHS Biomedical Advanced Research and Development Authority (BARDA), implemented the Influenza Vaccine Technology Transfer Initiative that included assistance to 11 DCVM chosen through a competitive grant process [390]. This initiative facilitated the transfer of technology for influenza vaccine production to the DCVM through an innovative technology platform, or technology "hub", where multiple DCVM members could access a centralized training facility to learn the basics of producing pilot-scale vaccine lots. Participants could then use this technical knowledge to scale up production in their own facilities[391]. As a result of this initiative, a number of developing countries have incorporated seasonal influenza vaccinations into their national immunization programs. Moreover, the technology "hub" model was also seen as a cost-effective mechanism for incorporating new vaccines into DCVM portfolios to increase immunization access [390].

HHS Leadership in Ensuring Global Influenza Manufacturing Capacity for Pandemic Influenza Preparedness

Augmenting global influenza vaccine manufacturing capacity to enhance pandemic preparedness protects both U.S. and global populations from the potential consequences of a severe influenza pandemic. These efforts have been a priority for HHS, and a number of HHS offices and agencies coordinate with WHO and many other global stakeholders to contribute to the GAP. These efforts also contribute to advance U.S. strategies for national pandemic preparedness. .

Since January 2010, the HHS Office of Global Affairs (OGA) has regularly partnered with WHO to conduct a series of workshops for governments, international donor organizations, academic institutions, vaccine manufacturers, and other key stakeholders on several topics including technology transfer, regulatory capacity building, global workforce development, health and economic impact of influenza, business modeling for sustainability, and communications on influenza vaccines as a mechanism to foster international collaboration and improve global influenza vaccine manufacturing capacity[392].

Table 4. Influenza Vaccine Manufacturing Workshops co-hosted by HHS/OGA and WHO

DATE	WORKSHOP TITLE	CITY
January 2010	Sustainable Influenza Vaccine Production Capacity Stakeholder's Workshop	Washington, DC, USA
September 2010	International Vaccine Technology Workshop	Hyderabad, India
June 2011	Workshop on International Regulatory Capacity Enhancement for Influenza Vaccines (WIRCEIV)	Sao Paulo, Brazil
November 2011	Workshop on Enhancing the Global Workforce for Vaccine Manufacturing	Cape Town, South Africa
June 2012	Workshop on Health and Economic Impact of Influenza	Bali, Indonesia
January 2013	Workshop on Business Modeling for Sustainable Influenza Vaccine Manufacturing	Washington, DC, USA
June 2013	Workshop on Enhancing Communication around Influenza Vaccination	Atlanta, GA, USA

These workshops have been attended by over 100 participants from more than 30 countries and provide opportunities to build and strengthen partnerships that are necessary for creating local, sustainable influenza vaccine manufacturing capacity. When viewed separately, individual workshops have addressed a main pillar necessary to build and maintain successful influenza vaccine manufacturing capacity. When viewed together, the series of workshop have cultivated broad contextual and societal support necessary to sustain vaccine manufacturing. The workshops have added value in that they have led to collaborations extending beyond pandemic preparedness. For example, the African Vaccine Manufacturers Initiative (AVMI), consisting of 12 African vaccine manufacturers, was launched at the September 2010 workshop in Hyderabad, India as a direct outcome of the workshop series. The goal of this group is *"...to develop and establish capacity in Africa for manufacture of vaccines and biologicals of assured quality and at affordable cost"*[393].

BARDA, part of the HHS Assistant Secretary for Preparedness and Response, has also assisted the WHO in expanding influenza vaccine manufacturing in 10 countries including Brazil, Egypt, India, Indonesia, Mexico, Romania, Russia, Serbia, Thailand, and Vietnam through US-based and on-site training workshops that provide technical assistance in the science, practice, and implementation of cGMP for influenza vaccine manufacturing[394]. For example, in 2011 BARDA collaborated with the WHO, Utah State University and North Carolina State University to initiate a series of three-week industry-focused training courses for DCVM to build core competencies in influenza vaccine production using cGMP[394,395]. Participants of these workshops are expected to use the information gained to implement influenza vaccine manufacturing and training of personnel within their own countries[395]. Efforts are also ongoing to work with WHO-grantees to support the development and testing of royalty-free adjuvants for use in pandemic vaccines[394].

HHS agencies continue to contribute to global influenza pandemic preparedness in a number of ways. The FDA/ CBER contributes to supporting influenza vaccine introduction in LMICs through its function as a WHO Collaborating Center for Biological Standardization and its work to build and strengthen the regulatory capabilities of NRAs in LMIC countries. To this end, FDA/CBER awarded a cooperative agreement to the WHO in 2011 as a mechanism to enhance technical cooperation between FDA, the WHO and Member States by providing NRA assessments, training programs for regulators, development of a WHO guideline for nonclinical evaluation of adjuvanted vaccines, and other regulatory capacity building activities intended to enhance global access to safe and effective vaccines[396].

Developing new and improved influenza vaccines that would enhance global preparedness is a high priority for NIH/NIAID. The NIAID influenza vaccine research program supports activities in a number of areas, including innovative technologies to improve production flexibility; more broadly protective vaccines; vaccines effective against newly emerging influenza viruses; adjuvant development, from early discovery to clinical evaluation; and safety and efficacy in special populations. NIAID is also working closely with academia and industry to explore the development of universal influenza vaccines based on highly conserved regions of the influenza virus. Such vaccines could obviate the need for annual reformulation and could be readily manufactured in the event of a pandemic.

NIAID's comprehensive influenza research program enabled a rapid response when the H1N1 influenza pandemic began in 2009. NIAID was able to swiftly evaluate the safety and immunogenicity of candidate H1N1 vaccines, conducting nine clinical trials that enrolled almost 3,900 volunteers. NIAID's prior evaluation of H5N1 vaccines established a framework for a coordinated, rapid response to H1N1. As a result, NIAID was instrumental in determining the doses needed to elicit protective responses to H1N1 in healthy adults as well as in special populations.

Incorporating the lessons learned from the 2009 H1N1 pandemic, the Global Action Plan for Influenza Vaccines II (GAP II) will continue to support developing country manufacturers in the development of new influenza vaccines.. The revised GAP II will include demand creation activities to complement the "push" mechanisms of direct assistance to manufacturers. CDC serves as the Implementing Partner for this part of the GAP-II plan. In this capacity, CDC leverages its international surveillance collaborations and research portfolio to transform disease burden data into communications and cost-effectiveness data that will allow Ministries of Health and international partners to make decisions about introduction and expansion of influenza vaccines. A key strategy is the International Vaccine Donation Program that is a public-private partnership between CDC, Walgreens, vaccine manufacturers, and several low income countries. This program allows low-income countries to receive vaccine and supplies, with support from CDC, to evaluate the safety and effectiveness of the vaccine. The country commits to developing a sustainable influenza vaccine program using the data and value created during the multi-year donation period. Fostering greater use of influenza vaccine in mid-income and developing countries will serve both USG's disease reduction goals and its pandemic preparedness priorities.

5. Strengthening the Capacity for Vaccine Decision Making

Introducing new and underutilized vaccines into national vaccine programs, combined with traditional vaccines, has the potential to save 23 million lives by 2020[11]. Yet, previous experience with the global introduction of the Hib vaccine demonstrates that unnecessarily prolonged delays in introduction can occur when decision-makers are unaware of the potential impact that a vaccine can have in improving the health of their populations[44].

Incorporating new and underutilized vaccines can positively affect national immunization programs, but the overall net benefits are often dependent on a country's ability to adequately plan for and finance

new vaccines and new technologies prior to their implementation[397,398]. Therefore, efforts to accelerate vaccine introduction into national immunization programs have focused on creating a systematic approach to vaccine decision-making by linking decision-making processes directly to an evidence base founded on vaccine need, cost-effectiveness, potential impacts on the overall health systems, and the vaccine's role in achieving national health priorities[399]. Once policies are implemented, the evidence generated by evaluating their introduction can be used to support those policies and further strengthen communications about the vaccines and to advocate for their uptake and sustained use by the community[400,401].

Developing an Evidence Framework for Decision-Making

NVAC Recommendation:

5.1 The ASH should continue to support the development of an evidence base to support informed country-level decisions regarding the development, introduction, and monitoring of new vaccines based on evaluation of disease incidence and prevalence, financial sustainability, safety, cost-benefits, and programmatic considerations.

Country-level decisions to support the introduction of new and underutilized vaccines can now be based on the greater abundance of the data expected to emerge from the improved systems that have been described throughout this report, including strengthening vaccine-preventable disease surveillance systems and vaccine pharmacovigilance activities. As previously noted, improved data collection and information sharing at the country level will help better establish evidence baselines for disease burden, calculate the predicted impact of vaccine introduction, and emphasize important safety signals and efficacy data expected in a given population. These data can then be used at all levels (i.e., global, regional, national) to prioritize public health efforts, justify financial commitments in vaccine research and development, and help build public demand for immunization.

In addition to disease burden and expected vaccine efficacy, countries may now consider vaccine introductions on a wider, more complex set of criteria that include economic, logistical, and social factors. These data will ideally represent each country's situation to best plan for vaccine acceptance and sustainability in the national immunization program over the long term[399,402,403]. The WHO has summarized the full scope of considerations within the 2005 guidance document *Vaccine Introduction Guidelines- Adding a vaccine to a national immunization programme: decision and implementation*[399].

Economic data and cost-effectiveness analyses are priority areas for most countries when considering investments in new vaccines or immunization technologies, but lack of access to this type of data is also cited as the biggest area of weakness in country-level decision making[403–406]. Following a series of training workshops conducted in 2004 and 2006 by PAHO, the WHO, CDC, and the Bill & Melinda Gates Foundation, Ministers of Health in PAHO's Directing Council Meeting requested that PAHO formalize a mechanism to assist PAHO member countries in better incorporating cost-effectiveness data into vaccine decision-making. The ProVac Initiative was formed in 2006 as a region-wide effort to provide technical assistance and resources to countries in Latin America and the Caribbean to better evaluate decisions to introduce new vaccines such as those against rotavirus, pneumococcus, HPV, and seasonal influenza[402,404]. The ProVac Initiative has supported 24 analyses in 14 Latin America and the Caribbean countries to implement the ProVac model in planning/forecasting their vaccine needs[407]. This has sparked an interest in other WHO member countries to expand this type of technical support to other low- and middle-income countries through the formation of ProVac International Working Groups, which facilitate information sharing and dissemination of analytical tools to countries outside of the PAHO region[408].

GAVI's Accelerated Vaccine Introduction Initiative (AVI)

At the end of 2008, based on lessons learned from investments in the accelerated development and introduction plans (ADIPs) for Hib, pneumococcal and rotavirus vaccines, the GAVI Alliance established the Accelerated Vaccine Introduction (AVI) initiative. Working through Alliance partners, the AVI is intended to facilitate a comprehensive approach to preparatory and introduction activities of GAVI supported vaccines, with an initial focus on rotavirus and pneumococcal vaccines and informing decision making at country level[456].

In 2012 the project shifted its focus to vaccine implementation, reflecting the need for GAVI to increase attention on the post introduction phase and expanding coverage following introduction.

These efforts are led by the GAVI Secretariat in partnership with the WHO, UNICEF, and the Vaccine Implementation Technical Assistance Consortium consisting of representatives from PATH, CDC, and the Johns Hopkins University, Bloomberg School of Public Health.

These partners contribute to country-level decision-making through numerous activities including, but not limited to, conducting pre-vaccine introduction assessments and post-introduction evaluations, developing communication strategies, providing logistical and management support, formulating policy guidelines and recommendations, establishing National Immunization Technical Advisory Groups, and reviewing applications for GAVI support. The AVI also provides staff support at the country- and regional-levels to assist in preparation for and implementation of GAVI funded programs[457].

In collaboration with the Bill & Melinda Gates Foundation, the PAHO ProVac Initiative has focused on providing participating countries with models and tools to conduct economic evaluations, financial sustainability assessments, and cost-effectiveness analyses[405,407–409]. For example, the On-Line International Vaccine Economics and Statistics (OLIVES) repository provides country-specific data on

disease burden, population demographics, healthcare utilization, healthcare costs, GDP per capita, and information related to vaccine coverage and immunization services (http://provac-olives.com).

In addition to the technical and economic information that informs vaccine decision-making, countries should also consider the logistical factors and operational criteria that could be impacted by new vaccine introductions such as possible effects on the vaccine supply chain or the availability of trained personnel[348,410,411]. Tools to examine and predict the potential impact of incremental changes to a country's national immunization program can help identify unanticipated costs, possible weaknesses, or potential bottlenecks in the vaccine supply chain that would impede their ability to successfully implement a new vaccine into their program. For example, CostVac, developed through the ProVac Initiative, helps to standardize the mechanisms for estimating the total cost of vaccine delivery within a country's routine immunization program. The CostVac tool accounts for all costs due to vaccines and supplies, personnel, and cold chain requirements and assists countries in establishing a baseline of expenditures for national immunization programs. These data are then used to more accurately forecast the financial impact that programmatic changes - such as adding a new vaccine- could have at each administrative level of the immunization program (e.g., central versus health facility level)[409]. Similarly, the Cold Chain Equipment Manager tool, developed through collaborations between PATH, UNICEF, WHO, and USAID, calculates the financial and programmatic costs that may be incurred by including a new vaccine or immunization technology into an existing supply chain[412].
Although local data and country-led efforts are important to building sustainable immunization programs, developing countries will still greatly benefit from ongoing scientific and technical support provided by WHO partner organizations.

In 2008, the WHO released guidance to countries for conducting economic evaluations of their immunization programs in preparation for introducing new and underutilized vaccines[413]. This document is intended to standardize the approach to economic analyses so that data shared between countries is transparent, complete, and comparable[413]. It emphasizes the need to present cost-effectiveness data in formats easily digestible by a range of immunization stakeholders and decision-making bodies. It also includes a summary of "attributes of good practice" and "questions for critical appraisals" to aid in improving the quality and usability of the analyses by creating a comprehensive checklist for data collection and evaluation[413]. The checklist can also point to knowledge gaps or areas where further research is needed.

In 2010, the WHO issued the Global Plan of Action for New and Underutilized Vaccines Implementation as a dynamic framework for WHO partner organizations to prioritize and implement programmatic and technical support activities to assist countries in gathering the data needed to inform country level decisions regarding new vaccines (e.g., generating guidance documents on optimal vaccine formulations/presentations to meet specific country needs)[414]. The specified focus areas include norms and standards; country decision-making; planning, financing, and procurement; vaccine delivery; integrated approaches to disease control; and monitoring and surveillance. In addition, the Action Plan outlines issues for partner agency assistance particular to each of the designated high priority vaccines including vaccines against Hib, pneumococcus, rotavirus, HPV, epidemic meningitis (MenA), Japanese Encephalitis, Yellow Fever, cholera, and typhoid. Considerations for coordination and support are also posed for dengue and malaria in preparation for future vaccines. This Global Plan of Action for New and Underutilized Vaccines Implementation is presented as a "living document" with the intention that it will be updated annually with input and lessons-learned from partner organizations based on their shared experiences and changing country needs[414].

Building Vaccine Decision Capacity through Expert Technical Advisory Groups

NVAC Recommendation:

5.2 The ASH should work with HHS offices and non-HHS partners to increase investments in national evidence-based decision making by National Immunization Technical Advisory Groups (NITAGs) (similar to the US Advisory Committee on Immunization Practices). Support should include technical assistance and provisions to develop and train these national immunization technical advisory bodies.

Apart from gathering the data that is needed to inform and support decisions about vaccine utilization and the introduction of new or underutilized vaccines, technical assistance and expert judgment is also needed to interpret, utilize, and translate this information into effective policies and strategies. To aid the WHO in setting global standards and developing immunization-related policy recommendations and guidance for its member states, the WHO established the Strategic Advisory Group of Experts (SAGE)[415]. SAGE is an independent advisory committee consisting of a multi-disciplinary group of technical experts that is mandated to provide evidence-driven recommendations, technical evaluations, and position statements on all aspects of vaccine-preventable diseases, vaccine research and development needs,

vaccine administration, immunization strategies and policies, and linking immunizations to other health interventions[415].

SAGE work products are often developed in close consultation with other WHO technical advisory committees such as the Global Advisory Committee on Vaccine Safety (GACVS), the Expert Committee on Biological Standardization (ECBS), the Immunization Practices Advisory Committee (IPAC), and the Quantitative Immunization and Vaccine-Related Research Advisory Committee (QUIVER). The resulting guidance is therefore comprehensive and represents a consensus opinion of the broader scientific and public health communities. Strong supporting evidence leads to strong WHO recommendations, which has been shown to greatly influence a country's willingness to implement new vaccines into their national programs[44].

Once approved, WHO recommendations may be used to inform country-level decisions and guide assistance programs, donor funding, and vaccine procurement priorities from organizations such as GAVI and UNICEF[415]. Further input advising on the incorporation of new vaccines and immunization technologies may also occur at the regional level through WHO regional Immunization Technical Advisory Groups (ITAGs). However, decisions to introduce and implement new or under-utilized vaccines into national immunization programs should ultimately occur at the country level, and WHO recommends that each country establish a National Immunization Technical Advisory Group (NITAG) to assist in country-led vaccine decision-making[321].

Though all countries are capable of making national-level decisions about vaccines and vaccine introduction, the capacity to develop evidence-based vaccine and immunization decision-making varies among countries. In one study surveying WHO member countries in 2008, NITAGs were reported in 89 of 147 countries (147 of 193 responded), with low and middle income countries least likely to report the presence of a NITAG[416]. Similarly, another 2008 survey looking at the Americas found 12 out of 35 PAHO countries lacked NITAGs[417]. Importantly, this study also found that many NITAGs lacked the necessary financial support from their governments. Moreover, several did not include a sufficient diversity of scientific disciplines among their members (e.g., clinicians, microbiologists, cold-chain logisticians) and none of the NITAGs in the Latin American and Caribbean countries included economic expertise[417]. Other analyses have also indicated that the processes and procedures used by individual NITAGs for developing recommendations and policies often differ between countries[416,418].

Several efforts are now underway to overcome these challenges by providing guidance for establishing NITAGs in countries that lack expert advisors and by providing tools to strengthen evidence-based decision-making in countries with existing NITAGs. As mentioned above, the PAHO ProVac Initiative works to assist PAHO-member countries in conducting evaluations of their national immunization programs based on defined technical, operational, social, and economic criteria. Technical support includes networking to academic ProVac Centers of Excellence (focused on decision science and policy research), regional training workshops, web-based resources, direct technical support when requested, and coordination with more established NITAGs[404,405,408]. For example, as part of ProVac coordination efforts, the CDC hosts delegations that include senior Ministers of Health and representatives from national immunization programs in PAHO countries to attend quarterly meetings of the CDC's Advisory Committee on Immunization Practices (ACIP)[419]. The participation of country delegations in the ACIP meetings is facilitated by staff from the PAHO Washington, DC office and supported by the Sabin Vaccine Institute. Attendance includes an orientation to the ACIP, introduction to the framework ACIP uses to establish its evidence-based recommendations[420], and working sessions devoted to strengthening country NITAGs.

Related efforts are being carried out by the Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) Initiative, which supports the establishment and strengthening of NITAGs in GAVI-eligible and middle income countries throughout Africa, Asia, the Middle East, and parts of Europe[421]. The SIVAC Initiative was formed in 2008 as a seven-year partnership between the French Agence de Médecine Préventive, the Bill & Melinda Gates Foundation, the WHO, and the South Korean International Vaccine Institute (http://www.sivacinitiative.org). SIVAC supports the establishment of NITAGs through a consultative process working directly with national health authorities, WHO, UNICEF, and others to make certain the necessary expertise is available to achieve evidence-based, country-driven decisions[421]. SIVAC provides support and technical assistance to countries to strengthen/improve NITAG efforts either through scientific/technical assistance to committee members or direct support to the secretariat with increasing responsibility shifted to the country to ensure long term sustainability[422]. In addition, SIVAC hosts an online resource center, hosts technical workshops, and conducts operational research to enhance the reach and impact of NITAGs.

Recently, SIVAC collaborated with the WHO and CDC to develop a set of performance indicators for assessing NITAGs[423]. These indicators are intended to help evaluate the impact of expert advisory committees on national immunization programs, to better understand their effectiveness, and to aid in activities to further strengthen national vaccine decision-making capacity. Over time these indicators may also be used to highlight best practices and guide the establishment of NITAGs in an even wider range of countries[423].

6. HHS Global Immunization Efforts: Leadership and Coordination

The culture of HHS is shifting toward a more institutionalized coordination of global health work as it has become widely accepted that the health of the U.S. is inextricably linked to the health of global populations. Global goals are now integrated into domestic goals, and strategies such as the HHS Global Health Strategy, the National Vaccine Plan, and the CDC's Global Immunization Strategic Framework are closely aligned with overarching global health initiatives such as the Decade of Vaccines Global Vaccine Action Plan (see appendix A). HHS shares its extensive technical expertise, exchanges best practices, and collaborates on health-related issues that contribute to a healthier, safer world, in partnership with other USG agencies engaged in global health.

Cultivating HHS Leaders in Global Immunizations

NVAC Recommendations:

6.1 The ASH should support on-going policy revisions to facilitate long-term assignment of HHS professional staff to international multilateral organizations, on bilateral assignments to support country Ministries of Health, and assignments to public-private global health partnerships, and other US federal agencies/departments.

The leadership of HHS in global health and global immunizations is apparent in its priorities, defined strategies, and participation in forums dedicated to identifying the best solutions to global health problems. HHS representatives serve as technical resources and delegates to a number of multilateral organizations and international initiatives. The HHS Secretary leads the U.S. delegation to the World Health Assembly, representing U.S. interests in global health issues including health security, international guidelines and standards, emergency response, and public health capacity building. HHS experts contribute to multiple aspects of the Decade of Vaccines, including a representative from

NIH/NIAID on the leadership council and HHS members of the Decade of Vaccines Steering Committee and working groups. Representative members from all HHS agencies also serve on expert committees, advisory committees, and technical panels for WHO including a number that have been described throughout this report.

Currently, HHS has over 300 staff stationed in 75 countries in support of advancing global health[424]. HHS has often seconded staff to multilateral organizations, Ministries of Health, other US government departments, and global health organizations, to accomplish critical global health work including in the area of immunizations. These have ranged from short-term details to long-term assignments, all within the bounds of HHS-wide policies regarding staffing, which are oriented primarily towards HHS's domestic health work and thus sometimes overlook the unique circumstances of global health undertakings.

Over the past year, efforts have been underway to revise the human resource policies to ensure that they are supportive of HHS' global health strategy and the Department's overall priorities, which include strengthening and expanding HHS health diplomacy capabilities. The ability to provide key technical and policy expertise to HHS partners, including in the area of vaccines and immunizations, is critical for international health cooperation efforts. Such assignments are also part of an HHS long-term effort to establish a more formalized global health career track, elements of which could be instrumental in the Department's ability to attract, deploy and retain key expert staff for global health activities.

Improving HHS Coordination across Global Immunizations

NVAC Recommendations:

6.2 As the director of the National Vaccine Program, the ASH should work with the HHS Secretary, the HHS Office of Global Affairs, and HHS Operating Divisions to define a process to strengthen coordination of HHS-led global immunization efforts. Enhanced coordination would ensure alignment of priorities, minimize duplication in global immunization efforts, support tracking progress in a consistent and transparent manner, and facilitate discussing and addressing challenges and barriers on an ongoing basis.

6.2.1 As part of these efforts, HHS should consider convening an HHS cross-departmental working group to create an HHS Global Immunizations Implementation Plan that includes: measurable outcomes defined by the HHS agencies, how the agencies will track progress towards these outcomes, and potential barriers to achieving the NVAC recommendations and other objectives described in Goal 5 of the National Vaccine Plan.

6.2.2 An HHS cross-departmental working group should also determine a mechanism to enhance HHS coordination with other USG agencies (e.g., USAID, DoD) and other critical non-USG partners (e.g., GAVI Alliance, UNICEF, WHO, the Bill & Melinda Gates Foundation, and others) for improved information sharing and decision-making on USG global immunization activities.

6.2.3 This HHS cross-departmental working group should also collaborate with USG agencies to understand how the whole of USG global immunization efforts are supporting implementation of the Decade of Vaccines Global Vaccine Action Plan, and identify areas where enhanced collaborations within HHS can increase the impact of US efforts.

HHS efforts towards global immunizations are many, and global health activities are now tightly woven into the day-to-day operations of many of the individual HHS agencies. However, it has been difficult to readily identify areas for enhanced collaboration between the HHS agencies due to the lack of a unified process for tracking HHS programs, projects, and progress. Better coordination of global immunization efforts within HHS would potentially multiply its impact by allowing agencies and staff offices to build off each other's progress, thereby enhancing HHS's global immunization efforts beyond the sum of its individual parts. Additionally, establishing a more institutionalized platform for coordination of activities can assist HHS in communicating its successes and global health service to leadership and the public. Finally, better coordination within HHS will also facilitate communicating about critical public health issues and departmental priorities, capabilities, and resources for global immunizations with other USG agencies (e.g., USAID) and other critical non-USG partners such as the GAVI Alliance, UNICEF, WHO, the Bill & Melinda Gates Foundation, and others.

Conclusion

Vaccines save millions of lives every year and are deemed one of the most cost-effective strategies in public health. As new vaccines become available and routine immunization systems are strengthened to

more effectively reach greater populations, the global health community has the potential to substantially reduce childhood mortality and alleviate the economic and societal burdens vaccine preventable diseases impose on nations around the world. Deemed the *Decade of Vaccines,* there is now a unique opportunity to build on the momentum of these and other global health efforts to ensure that all individuals and communities enjoy lives free from vaccine-preventable diseases.

The global immunization efforts described in this report demonstrate the power and reach these programs can achieve in improving global health for all people. In accordance with their charge, the NVAC has provided an analysis of the role of the U.S. Department of Health and Human Services (HHS) in global immunization efforts in order to identify key areas where HHS can best continue to contribute, consistent with the HHS Global Health Strategy and Goal 5 of the National Vaccine Plan.

These efforts showcase how the expertise housed within HHS is being applied to numerous important, yet unresolved, challenges in global immunizations. The NVAC believes HHS has a vital role to play in the global efforts to realize the *Decade of Vaccines* vision. The NVAC calls on the ASH to continue to make certain that global immunizations remain at the forefront of HHS global health priorities. HHS activities should take into consideration the available resources and how they can be applied to areas with the greatest opportunity to enhance global immunization programs. New HHS activities and collaborations should not adversely affect the funding or impede the progress of existing activities. As such, the NVAC submits these recommendations to the ASH for his consideration.

APPENDIX A: Mapping NVAC Recommendations to National and Global Immunization Strategies

Mapping NVAC Recommendations back to goals and objectives in the National Vaccine Plan, HHS Global Health Strategy, the CDC Strategic Framework for Global Immunizations, and the Decade of Vaccines Global Action Plan

For more information on the individual plans, please visit:
National Vaccine Plan: http://www.hhs.gov/nvpo/vacc_plan/
HHS Global Health Strategy: http://www.globalhealth.gov/global-programs-and-initiatives/global-health-strategy/
CDC Global Immunization Strategic Framework: http://www.cdc.gov/globalhealth/gid/framework/
Decade of Vaccines Global Vaccine Action Plan: http://www.dovcollaboration.org/action-plan/

Focus Area 1- Tackling time-limited opportunities to complete polio eradication and to advance measles mortality reduction and regional measles/rubella elimination goals
NVAC RECOMMENDATIONS 1.1 and 1.2
1.1 The Assistant Secretary for Health (ASH) should communicate to key audiences (including Capitol Hill and the general public) the urgency of completing global goals for polio eradication and advancing global measles mortality reduction goals and regional goals for measles/rubella elimination. The ASH should engage these key audiences via briefings, receptions, and other educational activities. 1.1.1 The ASH should emphasize that polio eradication efforts and measles mortality reduction and regional elimination efforts should complement and strengthen routine immunization systems. 1.1.2 The ASH should emphasize that failure to complete polio eradication goals or to advance goals for measles mortality reduction and regional goals for measles/rubella elimination may threaten the health of US populations due to importations of these diseases from endemic areas. 1.1.3 The ASH should emphasize that political and public support is fundamental to achieving polio eradication and advancing global goals for measles mortality reduction and regional goals for measles/rubella elimination. Achieving these goals would equal a monumental public health and humanitarian accomplishment for the entire global community and if done appropriately, will potentially strengthen support for routine immunization goals. 1.2 The ASH should strongly encourage the HHS Secretary to seek additional funding to ensure achieving unique time-limited opportunity to complete global goals for polio eradication and to support measles mortality reduction and regional goals for measles/rubella elimination. The ASH should advocate to the HHS Secretary that completion of these goals will yield significant economic and public health returns on investments and shed new light on the value of vaccines and immunization. Conversely, failure to reduce and/or eliminate these threats will require substantial ongoing financial and public health resources.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.2:** Support international organizations and countries to improve and sustain immunization programs as a component of health care delivery systems and promote opportunities to link immunization delivery with other priority health interventions, where appropriate. **Objective 5.6:** Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs **Strategy 5.6.1:** Participate in establishing global immunization priorities, goals and objectives and provide technical assistance at global, regional, and national levels.
HHS Global Health Strategy

Focus Area 1- Tackling time-limited opportunities to complete polio eradication and to advance measles mortality reduction and regional measles/rubella elimination goals
NVAC RECOMMENDATIONS 1.1 and 1.2
Objective 2: Prevent infectious diseases and other health threats
CDC Global Immunization Strategic Framework
Goal 1: Control, eliminate, or eradicate targeted VPD disability and death globally **Objective 1.1:** Achieve, certify, and maintain polio eradication **1.2:** Decrease global measles mortality and morbidity **1.3:** Accelerate global rubella control and congenital rubella syndrome (CRS) prevention **Goal 2:** Strengthen capacity and enhance performance of health systems to sustain delivery of routine immunization services.
Decade of Vaccines Global Vaccine Action Plan
Goal: Achieve a world free of poliomyelitis **Goal:** Meet global and regional elimination targets **Strategic Objective 4:** Strong immunization systems are an integral part of a well-functioning health system

Focus Area 1- Tackling time-limited opportunities to complete polio eradication and to advance measles mortality reduction and regional measles/rubella elimination goals
NVAC RECOMMENDATION 1.3
The ASH should encourage the Centers for Disease Control and Prevention (CDC) to continue to enhance the public health impact of its Stop Transmission of Polio (STOP) Program by increasing the number and length of training opportunities. STOP Team assignments should focus on building broad subject matter expertise that can be applied to polio and measles efforts, as well as to strengthen routine immunization systems and disease surveillance.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.1:** Support international organizations and countries to improve global surveillance for VPDs and strengthen health information systems to monitor vaccine coverage, effectiveness, and safety. **Strategy 5.1.1:** Achieve sustainable WHO certification quality surveillance for eradication of targeted VPDs. **Strategy 5.1.2:** Expand and improve sustainable surveillance systems for diseases having WHO-recommended vaccines and diseases for which vaccine introduction is being considered. **Objective 5.2:** Support international organizations and countries to improve and sustain immunization programs as a component of health care delivery systems and promote opportunities to link immunization delivery with other priority health interventions, where appropriate. **Strategy 5.2.1:** Provide technical support to countries, multilateral institutions, and other partners to strengthen key components of immunization program management and implementation, including epidemiological analysis, comprehensive planning, vaccine distribution and safe administration, monitoring, information systems, and program evaluation.
HHS Global Health Strategy
Objective 1: Enhance global health surveillance **Objective 2:** Prevent infectious diseases and other health threats **Objective 10:** Advance health diplomacy
CDC Global Immunization Strategic Framework

Focus Area 1- Tackling time-limited opportunities to complete polio eradication and to advance measles mortality reduction and regional measles/rubella elimination goals
NVAC RECOMMENDATION 1.3
Goal 1: Control, eliminate, or eradicate targeted VPD disability and death globally. **Objective 1.1:** Achieve, certify, and maintain polio eradication **1.2:** Decrease global measles mortality and morbidity **Goal 2:** Strengthen capacity and enhance performance of health systems to sustain delivery of routine immunization services. **Goal 3:** Strengthen VPD health information and surveillance systems to enhance decision-making capacity for immunization programs.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 2: Shared responsibility and partnership **Goal:** Achieve a world free of poliomyelitis **Goal:** Meet global and regional elimination targets **Strategic Objective 4:** Strong immunization systems are an integral part of a well-functioning health system

Focus Area 1- Tackling time-limited opportunities to complete polio eradication and to advance measles mortality reduction and regional measles/rubella elimination goals
NVAC RECOMMENDATION 1.4
The ASH should work with the CDC to create opportunities to bring together stakeholders and leadership from the Global Polio Eradication Initiative (GPEI) and the Measles Rubella Initiative (MRI) to discuss 1) lessons learned and best practices and 2) consider opportunities for joint programming that lead to program efficiencies and improve the delivery of vaccines using routine systems. As a leading partner in both these initiatives, CDC should work to capture and review these findings so as to inform current programming, the introduction of new vaccines, and other global public health efforts.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.6:** Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs **Strategy 5.6.1:** Participate in establishing global immunization priorities, goals and objectives and provide technical assistance at global, regional, and national levels.
HHS Global Health Strategy
Objective 2: Prevent infectious diseases and other health threats **Objective 7:** Identify and exchange best practices to strengthen health systems
CDC Global Immunization Strategic Framework
Goal 1: Control, eliminate, or eradicate targeted VPD disability and death globally **Objective 1.1:** Achieve, certify, and maintain polio eradication **1.2:** Decrease global measles mortality and morbidity **1.3:** Accelerate global rubella control and congenital rubella syndrome (CRS) prevention **Goal 6:** Build and strengthen partnerships that maximize coordination and synergy in meeting immunization goals **Objective 6.1:** Increase the capacity of global, regional, and national partnerships to effectively plan, coordinate, fund, and implement strategies for reaching global immunization goals.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 2: Shared responsibility and partnership **Goal:** Achieve a world free of poliomyelitis **Goal:** Meet global and regional elimination targets **Strategic Objective 4:** Strong immunization systems are an integral part of a well-functioning health system

Area of focus 2- Strengthening Global Immunization Systems

NVAC RECOMMENDATION 2.1

The ASH should advocate for HHS efforts that support USAID, GAVI, and multilateral organizations such as WHO and UNICEF in the development of "best practices" and technologies to support countries in their efforts to more accurately track immunization coverage at the national and subnational levels and improve data quality.

2010 National Vaccine Plan

Goal 5: Increase global prevention of death and disease through safe and effective vaccination.

Objective 5.1: Support international organizations and countries to improve global surveillance for VPDs and strengthen health information systems to monitor vaccine coverage, effectiveness, and safety.

Objective 5.2: Support international organizations and countries to improve and sustain immunization programs as a component of health care delivery systems and promote opportunities to link immunization delivery with other priority health interventions, where appropriate.

Strategy 5.2.1: Provide technical support to countries, multilateral institutions, and other partners to strengthen key components of immunization program management and implementation, including epidemiological analysis, comprehensive planning, vaccine distribution and safe administration, monitoring, information systems, and program evaluation.

Objective 5.6: Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs

Strategy 5.6.1: Participate in establishing global immunization priorities, goals and objectives and provide technical assistance at global, regional, and national levels

HHS Global Health Strategy

Objective 1: Enhance global health surveillance

Objective 2: Prevent infectious diseases and other health threats

Objective 7: Identify and exchange best practices to strengthen health systems

CDC Global Immunization Strategic Framework

Goal 3: Strengthen VPD health information and surveillance systems to enhance decision-making capacity for immunization programs

Objective 3.3: Increase the number of countries with information systems meeting the minimum quality criteria required to effectively monitor and manage immunization programs

Goal 6: Build and strengthen partnerships that maximize coordination and synergy in meeting immunization goals

Decade of Vaccines Global Vaccine Action Plan

Guiding Principle 2: Shared responsibility and partnership

Guiding Principle 5: Sustainability

Goal: Meet vaccination coverage targets in every region, country and community.

Strategic Objective 4: Strong immunization systems are an integral part of a well-functioning health system

Area of focus 2- Strengthening Global Immunization Systems

NVAC RECOMMENDATION 2.2

The ASH should work with other HHS offices to develop sustainable support for quality global vaccine preventable disease (VPD) surveillance systems, including the existing global and regional VPD laboratory surveillance networks. This support ideally should include technical and financial resources needed to support early warning/outbreak surveillance; laboratory diagnostics; emergency communication systems to detect and respond to outbreaks of vaccine-preventable diseases (VPDs); surveillance requirements for the eradication of targeted VPDs, including case-based polio, measles and rubella surveillance; and laboratory networks to support the introduction and monitor the impact of new and underutilized vaccines.

Area of focus 2- Strengthening Global Immunization Systems

NVAC RECOMMENDATION 2.2

2010 National Vaccine Plan

Goal 5: Increase global prevention of death and disease through safe and effective vaccination.

Objective 5.1: Support international organizations and countries to improve global surveillance for VPDs and strengthen health information systems to monitor vaccine coverage, effectiveness, and safety.

Strategy 5.1.1: Achieve sustainable WHO certification quality surveillance for eradication of targeted VPDs.

Strategy 5.1.2: Expand and improve sustainable surveillance systems for all diseases having WHO-recommended vaccines and diseases for which vaccine introduction is being considered.

Strategy 5.1.3: Strengthen all levels of global laboratory networks (including national, regional, and global reference laboratories) to sustain and improve VPD diagnosis in order to establish baseline disease burden, detect outbreaks, detect newly emerging variants of VPDs, and monitor the impact of new vaccines. This laboratory capacity should also be developed for surveillance of potential public health emergencies of international concern.

Objective 5.3: Support international organizations and countries to introduce and make available new and underutilized vaccines to prevent diseases of public health importance.

Strategy 5.3.1: Strengthen capacity at the country level, and in multilateral institutions as appropriate, to make informed decisions on introduction of new vaccines based on evaluation of epidemiology, financial sustainability, safety, and programmatic considerations, including support to national advisory committees.

HHS Global Health Strategy

Objective 1: Enhance global health surveillance

CDC Global Immunization Strategic Framework

Goal 1: Control, eliminate, or eradicate targeted VPD disability and death globally.

Goal 3: Strengthen VPD health information and surveillance systems to enhance decision-making capacity for immunization programs.

Objective 3.1: Increase the number of countries with access to proficient laboratory networks for vaccine-preventable diseases

Objective 3.2: Increase the number of countries with VPD surveillance systems that meet the minimum quality criteria required for program impact

Goal 4: Increase the appropriate development, introduction, and use of new and underused vaccines (NUVs) (e.g. Hib, pneumococcal, rotavirus, HPV, MenA, HepB birth dose, rubella, JE vaccine, cholera, typhoid, influenza, malaria, yellow fever) to prevent diseases of global and regional public health importance.

Objective 4.1: Increase the percentage of the global birth cohort that has access to NUVs as a part of a national immunization schedule and, within 5 years of introduction, achieve the same vaccination coverage level for NUVs as for other vaccines given at the same age.

Decade of Vaccines Global Vaccine Action Plan

Guiding Principle 2: Shared responsibility and partnership

Strategic Objective 4: Strong immunization systems are an integral part of a well-functioning health system

Area of focus 2- Strengthening Global Immunization Systems

NVAC RECOMMENDATION 2.3

The ASH should work with CDC and USAID to increase core support to the CDC's Field Epidemiology and Laboratory Training Program (FELTP) as a key tool to transferring epidemiologic and laboratory capacities for strengthening programs. This support should specifically be used to incorporate immunization topics into FELTP training.

2010 National Vaccine Plan

Goal 5: Increase global prevention of death and disease through safe and effective vaccination.

Area of focus 2- Strengthening Global Immunization Systems
NVAC RECOMMENDATION 2.3
Objective 5.1: Support international organizations and countries to improve global surveillance for VPDs and strengthen health information systems to monitor vaccine coverage, effectiveness, and safety. **Objective 5.6:** Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs.
HHS Global Health Strategy
Objective 1: Enhance global health surveillance **Objective 10:** Advance health diplomacy
CDC Global Immunization Strategic Framework
Goal 3: Strengthen VPD health information and surveillance systems to enhance decision-making capacity for immunization programs. **Objective 3.1:** Increase the number of countries with access to proficient laboratory networks for vaccine-preventable diseases.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 1: Country ownership **Guiding Principle 2:** Shared responsibility and partnership **Guiding Principle 5:** Sustainability **Strategic Objective 4:** Strong immunization systems are an integral part of a well-functioning health system

Area of focus 2- Strengthening Global Immunization Systems
NVAC RECOMMENDATION 2.4
The ASH should support the work of HHS within the international community to define standards for measuring the impact of routine delivery strategies such as the Reaching Every District (RED) strategy. These metrics can be used for the evaluation of how well these strategies perform in fully vaccinating children with routine immunizations.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.2:** Support international organizations and countries to improve and sustain immunization programs as a component of health care delivery systems and promote opportunities to link immunization delivery with other priority health interventions, where appropriate.
HHS Global Health Strategy
Objective 2: Prevent infectious diseases and other health threats. **Objective 7:** Identify and exchange best practices to strengthen health systems.
CDC Global Immunization Strategic Framework

Area of focus 2- Strengthening Global Immunization Systems
NVAC RECOMMENDATION 2.4
Goal 1: Control, eliminate, or eradicate targeted VPD disability and death globally. **Goal 2:** Strengthen capacity and enhance performance of health systems to sustain delivery of routine immunization services. **Objective 2.1:** Increase percentage of fully immunized children by 12 months of age. **Objective 2.2:** Increase immunization coverage with appropriate traditional and new vaccines among older-age children (>1 yr), adolescents, and adults. **Goal 6:** Build and strengthen partnerships that maximize coordination and synergy in meeting immunization goals. **Objective 6.1:** Increase the capacity of global, regional, and national partnerships to effectively plan, coordinate, fund, and implement strategies for reaching global immunization goals.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 3: Equity **Guiding Principle 5:** Sustainability **Guiding Principle 6:** Innovation **Goal:** Meet vaccination coverage targets in every region, country and community **Strategic Objective 3:** The benefits of immunization are equitably extended to all people **Strategic Objective 4:** Strong immunization systems are an integral part of a well-functioning health system

Area of focus 2- Strengthening Global Immunization Systems
NVAC RECOMMENDATION 2.5
The ASH should work with the Office of Global Affairs and CDC to assist national governments, development agencies (including USAID), multilateral organizations (including WHO and UNICEF), and civil society in encouraging the use of immunization contacts (both through routine systems as well as campaign activities) as a platform for delivering additional health services and vice versa. Evaluations of these efforts should include the types of interventions, the cost benefits of combining new interventions with global immunization efforts, and the effect these strategies have on building community demand for health services overall.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.2:** Support international organizations and countries to improve and sustain immunization programs as a component of health care delivery systems and promote opportunities to link immunization delivery with other priority health interventions, where appropriate.
HHS Global Health Strategy
Objective 2: Prevent infectious diseases and other health threats.
CDC Global Immunization Strategic Framework
Goal 5: Promote synergies between immunization programs and other public health interventions to strengthen health systems and contribute to decreased maternal and child mortality and morbidity. **Objective 5.1:** Increase the number of countries that have developed, implemented, and evaluated comprehensive national maternal and child health plans of action that appropriately integrate

Area of focus 2- Strengthening Global Immunization Systems
NVAC RECOMMENDATION 2.5
immunization with other priority health interventions.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 4: Integration

Area of focus 2- Strengthening Global Immunization Systems
NVAC RECOMMENDATION 2.6
The ASH should endorse HHS coordination with other USG agencies to support efforts that provide routine overseas administration and documentation of vaccinations for all US-bound refugees with vaccines that have been identified for pre-departure administration.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.6:** Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs. **Strategy 5.6.5:** Strengthen vaccination of globally mobile populations through targeted programs (e.g., pre-departure vaccination of US bound refugees)
HHS Global Health Strategy
Objective 2: Prevent infectious diseases and other health threats
CDC Global Immunization Strategic Framework
Goal 1: Control, eliminate, or eradicate targeted VPD disability and death globally **Goal 6:** Build and strengthen partnerships that maximize coordination and synergy in meeting immunization goals
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 2: Shared responsibility and partnership **Guiding Principle 3:** Equity **Strategic Objective 6:** The benefits of immunization are equitably extended to all people

Focus Area 3- Enhancing Global Capacity for Vaccine Safety Monitoring and Post-Marketing Surveillance
NVAC RECOMMENDATION 3.1
The ASH should identify mechanisms to encourage ongoing collaborations and technical support between HHS agencies involved in post-licensure vaccine safety and related global agencies and partners to 1) to enhance capacities to build vaccine safety surveillance systems to monitor the safety of vaccines as they are broadly administered; 2) to assess and respond to vaccine safety concerns or signals, effectively communicate vaccine risks; and 3) to support the political will to respond to vaccine safety concerns with evidence based decisions.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination.

Focus Area 3- Enhancing Global Capacity for Vaccine Safety Monitoring and Post-Marketing Surveillance
NVAC RECOMMENDATION 3.1
Objective 5.1: Support international organizations and countries to improve global surveillance for VPDs and strengthen health information systems to monitor vaccine coverage, effectiveness, and safety. **Objective 5.2:** Support international organizations and countries to improve and sustain immunization programs as a component of health care delivery systems and promote opportunities to link immunization delivery with other priority health interventions, where appropriate. **Objective 5.2.1:** Provide technical support to countries, multilateral institutions, and other partners to strengthen key components of immunization program management and implementation, including epidemiological analysis, comprehensive planning, vaccine distribution and safe administration, monitoring, information systems, and program evaluation. **Objective 5.2.4:** Introduce and improve programs that evaluation AEFIs. **Objective 5.4:** Support international organizations and countries to improve communication of evidence-based and culturally and linguistically appropriate information about the benefits and risks of vaccines to the public, providers, and policy-makers. **Objective 5.4.2:** Support the development of capabilities to communicate vaccine benefits and risks and to respond to emerging vaccine safety issues. **Objective 5.4.3:** Support national systems to improve reporting of adverse events.
HHS Global Health Strategy
Objective 1: Enhance global health surveillance **Objective 2:** Prevent infectious diseases and other health threats **Objective 3:** Prepare for and respond to public health emergencies **Objective 7:** Identify and exchange best practices to strengthen health systems
CDC Global Immunization Strategic Framework
Goal 2: Strengthen capacity and enhance performance of health systems to sustain delivery of routine immunization services. **Objective 2.4:** Promote safe immunization injection practices and develop country capacity to monitor and effectively investigate adverse events following immunization (AEFI). **Goal 3:** Strengthen VPD health information and surveillance systems to enhance decision-making capacity for immunization programs. **Goal 6:** Build and strengthen partnerships that maximize coordination and synergy in meeting immunization goals.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 1: Country ownership **Guiding Principle 2:** Shared responsibility and partnership **Guiding Principle 5:** Sustainability

Focus Area 4 - Building Global Immunization Research and Development Capacity
NVAC RECOMMENDATION 4.1
The ASH should support efforts that increase global health research capacity through partnerships between health research institutions in the U.S. and abroad. These partnerships create opportunities to train the next generation of U.S. and foreign scientists to better address current and future global health needs, including the development and evaluation of new vaccines, new vaccine delivery systems or immunization schedules, and new technologies that facilitate global immunization efforts.

Focus Area 4 - Building Global Immunization Research and Development Capacity
NVAC RECOMMENDATION 4.1
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.3:** Support international organizations and countries to introduce and make available new and underutilized vaccines to prevent diseases of public health importance. **Objective 5.6:** Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs. **Strategy 5.6.2:** Strengthen international collaborations for basic and applied research and related training of next generation researchers, especially in disease endemic areas, to include improving the stability and performance of current vaccines.
HHS Global Health Strategy
Objective 6: Catalyze health research globally **Objective 10:** Advance health diplomacy
CDC Global Immunization Strategic Framework
Goal 6: Build and strengthen partnerships that maximize coordination and synergy in meeting immunization goals. **Objective 6.1:** Increase the capacity of global, regional, and national partnerships to effectively plan, coordinate, fund, and implement strategies for reaching global immunization goals
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 1: Country ownership **Guiding Principle 2:** Shared responsibility and partnership **Guiding principle 6:** Innovation **Goal:** Develop and introduce new and improved vaccines and technologies **Strategic Objective 6:** Country, regional, and global research and development innovations maximize the benefits of immunization

Focus Area 4 - Building Global Immunization Research and Development Capacity
NVAC RECOMMENDATIONS 4.2 and 4.3
4.2 The ASH should encourage HHS agencies to work closely with USAID, WHO, end-users (including national immunization program managers, Ministries of Health, National Immunization Technical Advisory Groups), and vaccine manufacturers to support WHO in their efforts to define vaccine target product profiles. 4.3 The ASH should support NIH and FDA ongoing efforts to communicate strategies for minimizing barriers to the development of vaccine products. These efforts enhance the identification, testing, and evaluation of promising vaccine candidates to ensure candidate vaccines advance more quickly through the development pipeline.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.3:** Support international organizations and countries to introduce and make available new and

Focus Area 4 - Building Global Immunization Research and Development Capacity
NVAC RECOMMENDATIONS 4.2 and 4.3
underutilized vaccines to prevent diseases of public health importance. **Objective 5.6:** Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs.
HHS Global Health Strategy
Objective 2: Prevent infectious diseases and other health threats **Objective 6:** Catalyze health research globally
CDC Global Immunization Strategic Framework
Goal 4: Increase the appropriate development, introduction, and use of new and underused vaccines (NUVs) (e.g., Hib, pneumococcal, rotavirus, HPV, MenA, HepB birth dose, rubella, JE vaccine, cholera, typhoid, influenza, malaria, yellow fever) to prevent diseases of regional public health importance. **Objective 4.2:** Increase the number of new vaccines, improved vaccines, and combination vaccines that are prequalified by WHO for use in national immunization programs.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 2: Shared responsibility and partnership **Guiding principle 6:** Innovation **Goal:** Develop and introduce new and improved vaccines and technologies **Strategic Objective 6:** Country, regional, and global research and development innovations maximize the benefits of immunization

Focus Area 4 - Building Global Immunization Research and Development Capacity
NVAC RECOMMENDATION 4.4
The ASH should support efforts to strengthen national regulatory authorities in other countries through collaborations with the FDA. The ASH should also support on-going FDA efforts with other National Regulatory Authorities and the WHO to continue seeking opportunities to inform, shape, and communicate global regulatory standards and requirements for the development and manufacturing of safe and effective vaccines. In doing so, HHS will continue to strengthen international programs including building and strengthening global regulatory capacity and quality systems.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.5:** Support the development of regulatory environments and manufacturing capabilities that facilitate access to safe and effective vaccines in all countries. **Strategy 5.5.1:** Promote and support the efforts of WHO and other global partners to develop and harmonize international standards for vaccine development and licensure. **Strategy 5.5.2:** Promote and support the efforts of WHO and others to improve regulatory capacity in countries with limited infrastructures to assure vaccine quality, evaluate new vaccines when appropriate, and assure that clinical trials are conducted in accordance with Good Clinical Practices.

Focus Area 4 - Building Global Immunization Research and Development Capacity
NVAC RECOMMENDATION 4.4
Objective 5.6: Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs.
HHS Global Health Strategy
Objective 5: Strengthen international standards through multilateral engagement
CDC Global Immunization Strategic Framework
Goal 2: Strengthen capacity and enhance performance of health systems to sustain delivery of routine immunization services.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 1: Country ownership **Guiding Principle 2:** Shared responsibility and partnership **Guiding Principle 5:** Sustainability

Focus Area 4 - Building Global Immunization Research and Development Capacity
NVAC RECOMMENDATION 4.5
The ASH should support HHS agencies in their on-going efforts to develop training modules and workshops for vaccine manufacturers in developing countries on best practices and approaches for vaccine manufacturing and GMP guidelines.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.5:** Support the development of regulatory environments and manufacturing capabilities that facilitate access to safe and effective vaccines in all countries. **Strategy 5.5.3:** Provide technical assistance to developing country vaccine manufacturers to support development and production of safe and effective vaccines. **Objective 5.6:** Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs.
HHS Global Health Strategy
Objective 10: Advance health diplomacy
CDC Global Immunization Strategic Framework
Goal 6: Build and strengthen partnerships that maximize coordination and synergy in meeting immunization goals. **Objective 6.1:** Increase the capacity of global, regional, and national partnerships to effectively plan, coordinate, fund, and implement strategies for reaching global immunization goals.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 1: Country ownership **Guiding Principle 2:** Shared responsibility and partnership

Focus Area 4 - Building Global Immunization Research and Development Capacity
NVAC RECOMMENDATION 4.5
Guiding Principle 5: Sustainability

Focus Area 5- Strengthening Capacity for Vaccine Decision Making
NVAC RECOMMENDATION 5.1
The ASH should continue to support the development of an evidence base to support informed country-level decisions regarding the development, introduction, and monitoring of new vaccines based on evaluation of disease incidence and prevalence, financial sustainability, safety, cost-benefits, and programmatic considerations.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.3:** Support international organizations and countries to introduce and make available new and underutilized vaccines to prevent diseases of public health importance **Strategy 5.3.1:** Strengthen capacity at the country level, and in multilateral institutions as appropriate, to make informed decisions on introduction of new vaccines based on evaluation of epidemiology, financial sustainability, safety, and programmatic considerations, including support to national advisory committees.
HHS Global Health Strategy
Objective 2: Prevent infectious diseases and other health threats **Objective 7:** Identify and exchange best practices to strengthen health systems
CDC Global Immunization Strategic Framework
Goal 4: Increase the appropriate development, introduction, and use of new and underused vaccines (NUVs) (e.g., Hib, pneumococcal, rotavirus, HPV, MenA, HepB birth dose, rubella, JE vaccine, cholera, typhoid, influenza, malaria, yellow fever) to prevent diseases of global and regional public health importance.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 5: Sustainability **Goal:** Develop and introduce new and improved vaccines and technologies

Focus Area 5- Strengthening Capacity for Vaccine Decision Making
NVAC RECOMMENDATION 5.2
The ASH should work with HHS offices and non-HHS partners to increase investments in national evidence-based decision making by National Immunization Technical Advisory Groups (NITAGs) (similar to the US Advisory Committee on Immunization Practices). Support should include technical assistance and provisions to develop and train these national immunization technical advisory bodies.
2010 National Vaccine Plan

Focus Area 5- Strengthening Capacity for Vaccine Decision Making
NVAC RECOMMENDATION 5.2
Goal 5: Increase global prevention of death and disease through safe and effective vaccination. **Objective 5.5:** Support the development of regulatory environments and manufacturing capabilities that facilitate access to safe and effective vaccines in all countries. **Strategy 5.5.2:** Promote and support the efforts of WHO and others to improve regulatory capacity in countries with limited infrastructures to assure vaccine quality, evaluate new vaccines when appropriate, and assure that clinical trials are conducted in accordance with Good Clinical Practices.
HHS Global Health Strategy
Objective 5: Strengthen international standards through multilateral engagement **Objective 10:** Advance health diplomacy
CDC Global Immunization Strategic Framework
Goal 2: Strengthen capacity and enhance performance of health systems to sustain delivery of routine immunization services. **Objective 2.3:** Increase the percentage of countries with a well-functioning (based on WHO criteria) National Immunization Technical Advisory Group (NITAG) with capacity to make evidence-based decisions on immunization policy and programs, including epidemiologically appropriate introduction of new and underused vaccines.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 1: Country ownership **Guiding Principle 2:** Shared responsibility and partnership **Guiding Principle 5:** Sustainability

Focus Area 6 - HHS Global Immunization Efforts: Leadership and Coordination
NVAC RECOMMENDATION 6.1
The ASH should support on-going policy revisions to facilitate long-term assignment of HHS professional staff to international multilateral organizations, on bilateral assignments to support country Ministries of Health, public-private global health partnerships, and other US federal agencies/departments.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination **Objective 5.6:** Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs. **Strategy 5.6.1:** Participate in establishing global immunization priorities, goals, and objectives and provide technical assistance at global, regional, and national levels.
HHS Global Health Strategy
Objective 10: Advance health diplomacy

Focus Area 6 - HHS Global Immunization Efforts: Leadership and Coordination
NVAC RECOMMENDATION 6.1
CDC Global Immunization Strategic Framework
Goal 6: Build and strengthen partnerships that maximize coordination and synergy in meeting immunization goals.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 2: Shared responsibility and partnership

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Focus Area 6 - HHS Global Immunization Efforts: Leadership and Coordination
NVAC RECOMMENDATION 6.2
6.2 As the director of the National Vaccine Program, the ASH should work with the HHS Secretary, the HHS Office of Global Affairs, and HHS Operating Divisions to define a process to strengthen coordination of HHS-led global immunization efforts. Enhanced coordination would ensure alignment of priorities, minimize duplication in global immunization efforts, support tracking progress in a consistent and transparent manner, and facilitate discussing and addressing challenges and barriers on an ongoing basis. 6.2.1 As part of these efforts, HHS should consider convening an HHS cross-departmental working group to create an HHS Global Immunizations Implementation Plan that includes: measurable outcomes defined by the HHS agencies, how the agencies will track progress towards these outcomes, and potential barriers to achieving the NVAC recommendations and other objectives described in Goal 5 of the National Vaccine Plan. 6.2.2 An HHS cross-departmental working group should also determine a mechanism to enhance HHS coordination with USG agencies (e.g., USAID, DoD) and other critical non-USG partners (e.g., GAVI Alliance, UNICEF, WHO, the Bill and Melinda Gates Foundation, and others) for improved information sharing and decision-making on USG global immunization activities. 6.2.3 This HHS cross-departmental working group should also collaborate with USG agencies to understand how the whole of USG global immunization efforts are supporting implementation of the Decade of Vaccines Global Vaccine Action Plan, and identify areas where enhanced collaboration can increase the impact of US efforts.
2010 National Vaccine Plan
Goal 5: Increase global prevention of death and disease through safe and effective vaccination **Objective 5.6:** Build and strengthen multilateral and bilateral partnerships and other collaborative efforts to support global immunization and eradication programs.
HHS Global Health Strategy
Objective 10: Advance health diplomacy
CDC Global Immunization Strategic Framework
Goal 6: Build and strengthen partnerships that maximize coordination and synergy in meeting immunization goals.
Decade of Vaccines Global Vaccine Action Plan
Guiding Principle 2: Shared responsibility and partnership

Focus Area 6 - HHS Global Immunization Efforts: Leadership and Coordination
NVAC RECOMMENDATION 6.2

APPENDIX B: An Example of a Target Product Profile

Sample Courtesy of the Bill & Melinda Gates Foundation

Attribute	*Sub-Attribute*	Desired (Best) Target	Acceptable Target	Minimally Acceptable Target	Comments
Indication	*Prophylactic Objective* *Target population*				
Efficacy	*Clinical microbiology* *Protective magnitude* *Duration of protection*				
Clinical Immunology	*serum* *mucosal* *Challenge*				
Dosage and Administration	*Route* *Volume* *Schedule of administration*				
Formulation	*Potency* *Form/State* *Adjuvantation*				

Attribute	*Sub-Attribute*	Desired (Best) Target	Acceptable Target	Minimally Acceptable Target	Comments
Storage/ Handling	*Product presentation/ packaging* *Space/Volume consideration* *Preservative* *Shelf-life (temp/time)* *(Cold Chain requirements)*				
Safety	*Non-clinical toxicology* *Over-dosage* *Adverse Reactions* *SIAs* *Precautions/Warnings/Contraindications/ Drug interactions* *Medical waste disposal*				
Use in special populations	*Pregnancy* *HIV(+)*				
Product registration and WHO prequalification					
Time	*Time to Proof-of-concept*				

Attribute	*Sub-Attribute*	Desired (Best) Target	Acceptable Target	Minimally Acceptable Target	Comments
	Time to IND submission *Time to licensure/ prequalification*				
Supply	*Max. Price to purchase (per course)* *Prequalified suppliers* *Tech transfer*				
Manufacturing material	*Antigen* *adjuvant*				
	Costs of consumable goods				
Manufacturing /yield	*Expression systems* *Versatility of production*				
Delivery method	*Skill/Training level of health worker* *(and strength requirements/ergonomic issues)* *Device*				
	Device safety features				
	Device -Cost/dose delivered (re-usable parts including consumables)				

Attribute	*Sub-Attribute*	Desired (Best) Target	Acceptable Target	Minimally Acceptable Target	Comments
	Device - Required accessory materials				
	Device: # uses/re-usable device				
	Single (dedicated) or multiple volume or depth delivered/settings				
	Single vaccine product or multivaccine product ability				
Other isssues	*Global Access Issues*				

APPENDIX C: National Vaccine Advisory Committee Global Immunization Working Group Members

NVAC Working Group Co-chairs
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Professor of Clinical Pediatrics
Columbia University

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Executive Director
Every Child by Two

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Bill & Melinda Gates Foundation
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Developing Country Vaccine Manufacturers Network
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Claudia Vellozzi, CDC
Michel Zaffran, WHO
Patrick Zuber, WHO

APPENDIX D: NVAC Resolution Establishing the Global Immunizations WorkingGroup

Approved Resolution by the National Vaccine Advisory Committee (8 February 2012)
Regarding the Establishment of NVAC-Global Immunization Working Group

Preamble
Goal 5 of the U.S. 2010 National Vaccine Plan specifies that the U.S. should increase efforts towards global prevention of death and disease through safe and effective vaccination. The role of the U.S. government in global vaccination should be reviewed to ensure that we are on track to fulfill our responsibilities and meet these goals and objectives.

Resolved,
The National Vaccine Advisory Committee (NVAC) charges a Working Group with the tasks of "**reviewing the role of HHS in global vaccination, the effects of global vaccination on global populations, the effects of global vaccination on US populations, and recommend how HHS can best continue to contribute, consistent with its newly established Global Health Strategy and Goal 5 of the National Vaccine Plan. The working group should also make recommendations on how to best communicate this information to decision makers and the general public to ensure continued sufficient resources for the global vaccination effort".**

The Working Group should complete its work and make its report to NVAC by the February 2013 meeting. This report should provide recommendations to the Assistant Secretary of Health on how to implement the recommendations.

Votes for the Resolution:
14 NVAC Members Present (3 via teleconference):
Votes: 14 in favor; 2 NVAC members absent.
Resolution passed and approved by NVAC on 8 February 2012 at 1215 EST

Note: NVAC Chair, Dr. Walter Orenstein, designated NVAC member Dr. Philip LaRussa as the Chair of the NVAC- Global Immunization Working Group.

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